

HOST RESISTANCE TO CANCER
REVIEW OF THE EARLY AND
RECENT LITERATURE

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"Spontaneous" Regression in which there was concurrent fever, leukocytosis following confinement:

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INTRODUCTION

Until the past 15 years the importance of host resistance factors in the overall management of cancer was largely ignored. The data assembled here may help to stimulate further research on this most hopeful approach to the cancer problem.

This review includes abstracts of most of the significant reports appearing in the last 80 years relating to spontaneous regression and tumor immunity. Everson and Cole (1956) define spontaneous regressions as the partial or complete disappearance of a malignant tumor in the absence of all treatment, or in the presence of therapy considered inadequate to exert a significant influence on neoplastic disease. However, as Nauts, Pelnor and Fowler (1958-1970) have pointed out, it appears that spontaneous regressions in the literature are not truly spontaneous but are almost always associated with certain concurrent "complications" such as acute inflammatory, febrile or infectious episodes. They have occurred more frequently in patients receiving fever therapy, heat, bacterial toxin therapy or some other host-stimulating agent such as BCG or zymosan.

The older data herein reviewed suggests the important role of acute inflammation in resistance to cancer whether it was produced accidentally by concurrent erysipelas, bee stings or by various acids, chloride of zinc, iodine, turpentine, silver salts, actual cautery and electrocautery, lightning, and thermal burns, or vesicants.

DEFENSE MECHANISMS OF THE BODY AGAINST CANCER

Rubens Duval (1914), in discussing the defense mechanisms of the organism against cancer, noted that up to 1909 it was classic to consider that the tissues of the body allowed themselves to be destroyed by neoplastic proliferations without opposing any resistance to their invasion. The cases of regression and perhaps of spontaneous cure of malignant tumors which had been reported did not seem entirely convincing and the diagnoses were considered equi-

vocal. Thereafter the investigations of a number of authors on experimental tumors in animals have made it possible to verify many cases of spontaneous cures. Clunet (1910) reported several in his remarkable thesis. New observations published with thorough histologic examinations do not permit any doubt as to the possibility, in man also, of spontaneous regression, at least temporary and partial, of malignant neoplasms. He cited Petit and Mouchet (1905), Kaposi (1901), Sampson Handley (1909), Baum (1911), Hess (1913), Broechaert (1913), Theilhaber (1912), Ribbert (1911), Gideon Wells (1909), De Pace (1912).

Nevertheless, the human observations are few and one might be tempted to conclude that they are exceptions which do not invalidate the ancient classic conceptions. In reality the cases of regression are the visible clinical manifestations of a process of spontaneous cure which one finds frequently when one searches systematically for the indications.

Rubens Duval asked if spontaneous regression is due to a veritable defense mechanism of the organism. He analysed the changes observed:

Connective Tissue, Vascular and Leukocytic Reactions: Sclerosing type of reaction, regarded by Handley as the essential factor in spontaneous regression of tumors, i.e., fibrosis. This simple defensive reaction opposes only a temporary and inadequate barrier which soon becomes invaded by the neoplasm.

Lymphoid Reaction to Neoplasms: All around cancerous proliferations there appears a more or less thick layer of lymphoid tissue, due to the supply of mononuclears and to the transition of connective tissue into reticular tissue. When this reaction is well developed, there is not merely an increased supply of mononuclears, but also the appearance of the germinative cells of Flemming and even of tumefaction of the lymphopoietic centers. The latter actively produce mononuclears which come to add themselves to those of the lymphoconnective tissue which have migrated.

This lymphoid reaction is observed in non-ulcerated and non-infected tumors. It is therefore directly invoked by the development of cancer. It does not produce itself only in the immediate periphery of a cancer lesion but also at a distance, in

the lymph nodes of the affected area. These become enlarged even though they have no evidence of metastatic involvement.

The lymphoid reaction doubtless opposes itself less to the proliferation of epithelial cells than to the diffusion of toxic cancerous substances. In any case cancer cells can be modified in their nutrition and one can observe here and there phenomena of evolutive maturation (see below).

The lymphoid reaction, by its reserves of lymphoconnective tissue cells which are accumulated around cancer lesions, is ready to utilize the therapeutic measures which one may furnish the organism. Also, when one observes this lymphoid reaction in a case which appears to be clinically possible to treat with radium, one may predict that the chances of obtaining a successful result are very good.

Suppuration: Suppuration is, in effect, the strongest defense mechanism which the organism can set up. When one finds a neoplasm whose cells are capable of conserving their vitality when surrounded by pus, the prognosis is grave.

Rubens Duval believed that when a neoplasm has been present in a patient for some time, the organism is not sufficiently irritated by the neoplastic cells alone to react against them by an acute or even a subacute inflammatory reaction, but that it becomes able to do so by means of a slight microbial irritation. The latter stimulates and develops the reactive ability. All the conditions which facilitate the penetration of the microbes of secondary infection also enhance the development of acute or subacute inflammation. The effect of this inflammatory reaction on epitheliomatous cells is in general very marked. The prognosis as regards the use of radium becomes excellent when the majority of cancer cells are involved in an inflammatory process.

Eosinophilic Reaction: This reaction is a modality distinctive of the subacute inflammatory reaction. The exact importance of eosinophilia is not understood. Frequently it is highly developed in epithelioma of the lower lip, but it is in the neoplasms of the genital organs in which it reaches its maximum: cancer of the ovary and pavement cell epithelioma of the uterus.

Reaction of the Polynuclear Neutrophile Type: This type may vary from the arrival of a few polynuclears up to an acute suppurating inflammation. It is rare that suppuration involves all the tumor. Rubens Duval cited a case of this type in which suppuration developed prior to surgical removal. This acute inflammation did not prevent recurrence of the tumor. Nevertheless, microscopic examination of the tumor specimen revealed modifications in most of the epitheliomatous cells: decrease in protoplasm and phenomena of evolutive maturation. These changes indicated the effects of the unfavorable soil produced by the suppuration. Rubens Duval believed that these modifications played an important role in the successful later treatment of the recurrence with radium. (The recurrence was also severely infected.) Complete and permanent regression followed the radium treatment. He added: "The enhancing action of the suppuration is all the more probable, since epithelioma is one of the tumors which as a general rule is only slightly radiosensitive.

The Degree of the Inflammatory Reaction: It is an important point in determining the probable action of radium, and the appreciation of its importance is, in a certain degree, apt to correct the impression which is given by merely studying the cancerous elements.

Modifications of Epitheliomatous Cells: When in untreated tumors one observes evidence of necrosis or of inhibition of growth associated usually with the above-mentioned defense mechanisms, and occasionally when these reactions appear mild, the characteristics of cellular injury extend to almost all the tumor, thus indicating that the tumor is growing in a soil that is unfavorable to its development, due either to inherent or acquired humoral conditions.

Ménétrier admitted a modification of the nutrition of the cellular elements under the degenerating substance in the body, perhaps produced by the cells of the organism as a reaction against the neoplastic elements.

In conclusion he stated: "The phenomena of spontaneous regression of cancers and the defense reactions of the organism are not of merely theoretical interest. Each time complete surgical removal is impossible, one can only hope for regression of the remains of the neoplasm if one can injure the cancerous elements and reinforce

the resistance of the organism. It is then quite apparent that if a biopsy reveals suggestions of spontaneous regression, these, even though minimal, give a more favorable prognosis. The treatment then instituted will have a greater chance of proving effective when the organism will be more capable of using its adjuvant benefits."

(Rubens Duval, 1914)

Tumor Immunity

Rubens Duval (1920) discussed at length the local and systemic defensive powers of the organism against cancer.

"When cancer is established with all its clinical and histological characteristics of malignancy, the organism, even though having suffered a grave defeat, does not usually cease to battle against the invader. In exceptional cases, it may do so with sufficient success so that a spontaneous regression occurs."

He then cited Pearce Gould's case as being one of the most remarkable: a woman who had been operated upon in 1890 for cancer of the left breast, proven histologically, and by 1895 had a local recurrence in the scar, numerous cutaneous, axillary and supraclavicular metastases, also osseous metastases with a pathological fracture of the left femur. Then in 1896 without any treatment, the nodules healed, the fracture united and all trace of the tumor disappeared. In 1896 the cicatrices remained supple and the general health was excellent.

"Many other cases of spontaneous regression have been reported by Clement, Petit and Mouchet, Kaposi, Sampson Handley, Baum, Hess, Broekaert, Theilhaber, Ribbert, Gideon Wells, De Pace, etc.

"These cases cannot be doubted, but they are exceptional because there is really very little chance that an organism which has let itself be invaded by cancer can spontaneously become capable of overcoming the cancer, since (the resisting power of) the organism has been exhausted by the disease.

"On the other hand, when the organism is relieved in its struggle by surgical intervention or by some other aid, it can, by this aid and stimulation of its reactions, complete what these could not have done unaided.

"Thus, J.L. Faure has observed more than once that incomplete excision of a very

extensive neoplasm is followed by cure. Mme. Laborde and Cuel have observed the regression of a chondroma after inadequate radiation. Darier has obtained partial and even complete regressions of metastatic nevocarcinomas after electrolysis of the primary growth.

"An accidental concurrent bacterial infection, as well as incomplete excision or radiation, may stimulate a useful defensive reaction in cancer patients. These infections sometimes produce a suppuration which neither the cancer cells nor the microbes of secondary infections, usually of slight virulence, would have been able to produce. When cancer has already existed for a certain length of time, the organism is insufficiently irritated by the neoplastic cells alone to react by an acute or subacute inflammatory process, as it does in the initial stages of a tumor, but it regains this power following the stimulus of a microbic infection.

"The tumors which remain benign because they are well compensated, the malignant tumors which grow slowly and sometimes present long periods of remission, the tumors which do not recur or in which the metastases only develop long after removal of the primary neoplasm - all these facts often and easily observed - are they not evidence of obstacles which the organism places against the neoplastic cells?"

Analysis of the Defense Reactions: Rubens Duval stated that tumor cells and normal cells react upon one another. By the general circulation, by the action of the nervous system, the divers areas of the organism are associated in the battle against cancer.

Local Reactions: The cancer manifests itself by a lack of equilibrium which tends to become progressively more accentuated. The organism tends to reestablish the equilibrium especially by means of compensatory reactions of the connective tissue. The less serious types of neoplasms are those in which the connective tissue stroma is abundant and vigorous. The most malignant forms are those in which the stroma is reduced to a few pock-marked trabeculae poor in cells and more or less gravely altered.

The local reaction of the organism against cancer is essentially a lymphoid-connective tissue reaction. For the cases where this reaction is well-developed the connective tissue in the region where cancer cells are proliferating is transformed

into a reticulated tissue. This transformation results partly from the loss of differentiation of the fibroblasts, etc., followed by functional adaptations and new differentiations, and partly by the immigration of young lymphoconnective tissue cells by the vascular route. Thus the cutaneous, the fibrous and the adipose tissue of the hypodermis or any one of the connective tissues of the organism is transformed into lymphoid tissue. This lymphoid transformation may be only rudimentary, in which case it reduces itself to a few groups of migratory cells, infiltrated here and there, especially around the blood vessels. It can result in the formation of a continuous sheet of lymphoid tissue completely surrounding the neoplasm. The defense of the organism can perfect itself further: in the lymphoid tissue sheet at the periphery or in its immediate vicinity, but always at a distance at first from the neoplastic plug, there is formed germinative centers having the same structures as those of the lymph nodes and solitary lymphatic nodules. They differ from normal follicles only by the absence of lymphatic vessels. These newly formed follicles produce in situ the lymphatic cells which are useful in the defense against cancer.

As needed, these will be variously employed: the lymphoid tissue thus formed is at once a living barrier which partially isolates the tumor area, and a filter which regulates the humoral exchanges between this area and the other parts of the organism. It also pours into the area the products of secretion resulting from the activity of its constituent cells.

Sometimes the immigration of polynuclear neutrophiles occurs and the reaction takes the form of an acute inflammatory process which may result in suppuration. This, if it is moderate, and if it only produces the disintegration of the necrotic tumor cells, is altogether favorable and liquifies the remains of the tumor. But if it is too active, if it produces a sudden disintegration of the cancer cells, it is more dangerous than useful, because the neoplastic poisons thus liberated by brusque cytolysis gravely affect the connective tissue and provoke fibrinoid necrosis. The defenses of the organism are then inhibited and the malignancy of the cancer increases.

At other times, the lymphoid tissue differentiates itself into fibroblasts which elaborate collagen. . . . This fibroblastic reaction may result either in a

hypertrophic sclerosis, a veritable fibroma, or in simple fibrous barriers.

Whenever a marked connective tissue reaction is produced, it is accompanied by a production of newly formed blood vessels. This appears to be greatest at the points where the struggle is keenest.

Rubens Duval then noted the effects of radiation. He stated: "It is probable that the effectiveness of radiotherapy is due as much to the lymphoid connective tissue reactions it provokes as to the destructive effects it may produce on the cancer cells. What proves this is that when radiation has been excessive in certain areas, and has affected not only cancer cells, but the connective tissue cells, the neoplastic proliferation though temporarily arrested, does not take long to renew its activity. We have seen cancer recur in the areas of radiation necrosis which have been deprived of all means of defense, although the cancer cells completely disappeared from the areas less heavily radiated, which were reactive. As Mme. Fabre has remarked: 'It is often noted that the neoplastic elements entirely disappear from the periphery of the tumor while islands of cancer persist in areas that have received 5 to 10 times a higher dose of radiation.'

"She further stated: 'One cannot have an effective radiotherapy when the connective tissue is deficient.'

"Roussy and Leroux go further and declare that 'radium therapy employed with the technique and the usual doses may have a harmful effect.'

Proust, as regards irradiation of cancers of the skin, has observed that when it is excessive it may be harmful, as it is capable of inhibiting the connective tissue.

Roussy and Leroux have indicated that radiation is especially dangerous when the defense reactions are already precarious or insufficient. These authors and Mme. Simone Laborde and E. Peyre use biopsies and blood examinations for indications and prognosis of radiation.

Rubens Duval then discussed the Lymph Node Reactions and finally the Humoral Reactions to cancer. He described the work of Murphy and his group, and concluded that it seemed proven that the lymphocytes are necessary in the defense reactions of

the organism against cancer. He believed that the thyroid gland seemed to play an important role in the development of tumors. In dogs thyroidectomy stimulates neoplastic growths, in rats the addition of thyroid to the diet causes considerable retardation of tumor growth. Action is more evident with small doses. In patients with cancer, Odie and Girard have observed the frequency of hypothyroidism, as well as the good effects of thyroid opotherapy. Naamé often found signs of hypothyroidism in breast cancer and obtained good results in such cases by combining thyroid and mammary organotherapy. Page and William Bishop published a case of a cure of recurrent cancer of the breast after treatment with thyroid extract.

The influence of other glands is less well established. The study of the blood may enable us to predict and follow the general reactions of the organism during treatment.

Reactions of the Nervous System: The functioning of the organs depends on the nervous system, whose role appears to be considerable. Innumerable authors have reported how frequently one observed that cancer has developed following a profound sorrow, reverses of fortune, grave moral or material anxieties, an overstrain or any cause of nervous depression. It is no less remarkable to note that the patients who defend themselves the best against their cancers are those who want to do so. The will to live manifests itself with much more force and energy, while those who are hopeless, either because they are depressed by their condition, their infirmities, or who fear still more terrible afflictions, or have lost a desire to live - these do not resist cancer, and are carried away rapidly by it.

Certain clinical observations make us think that, on the other hand, certain toxic products of cancer are perhaps poisons of the nervous system.

Conclusions: A study of the defense mechanisms of the organism against cancer gives one a better understanding of the various modalities of the structure and evolution of tumors. In any case, it has considerable practical application. For those who do not consider these reactions, there is no other therapeutic measure except that which consists of destroying the cancer by excision entirely beyond the supposed

limits of the disease. This approach leads surgery to more and more extensive excisions, progressively more mutilating. The more radical operative procedures are not by any means always compensated by a lessened frequency in recurrences. Odier estimates that following the conservative operations of the older surgeons, because of the lack of asepsis, the wound did not heal by first intention, and these operations were less often followed by recurrences. There is then produced an acute inflammatory reaction sufficient to produce cytolysis and disintegration of the cancer cells remaining in the tissues.

This same approach, that ignores the defense mechanisms, leads radiologists to deliver more and more extensive and intensive radiation therapy without the benefit being always very apparent. It would seem even that, as DuPont and Leroux have noted, that sometimes quite the reverse is true. When the defense reactions are already mediocre or precarious, heavy radiation destroys them and the cancer cells are liberated from all barriers and develop unchecked.

Or, if we do consider the defense mechanisms, while the cancer is localized, one may hope, in stimulating and sustaining them, that we may complete what surgery and radiotherapy have left undone and thus we may increase the chances of cure. Even when the cancer is generalized, we are no longer completely disarmed. By chemotherapy, we may still combat the disease with more or less success.

If one believes in these defense reactions, we will search for them and find them, and learn to use them in diagnosis, prognosis and treatment of cancer by means of biopsies and blood studies. (Rubens Duval, 1920)

Spontaneous Regression

Rubens Duval (1938) stated that cancer is a disease so recurrent that a surgical removal, as a general rule, can be curative only if it is possible to produce total destruction of all the neoplastic cells. Nevertheless, in certain cases an incomplete excision is followed by apparent cure of long duration or even by a really definitive cure.

Bovier (1938) reported several such cases.

Touraine and Duperrat (1938) published a very well-documented article on spon-

taneous cure of cancer (see below).

Rubens Duval believed that true immunity to cancer resulted not from surgical removal of the cancerous elements, but by resorption of the cancer cells.

He cited Besredka's experiments in producing immunity to the Shope rabbit papilloma by intracutaneous inoculations of a small dose of an emulsion of these same tumors. While subcutaneous injections were followed by the development of neoplasms which caused death of the animals, intradermal inoculations caused the development of a tumor which soon ceased to grow and regressed spontaneously and completely. An immunity was then acquired and the animal was refractory to further inoculations into skin, peritoneum, testicle, brain or the anterior chamber of the eye. This immunity is specific and does not prevent the development of other types of tumors such as tar tumors. It is, of course, a very different matter to immunize a healthy animal against a cancer transplant and to attempt to obtain in man suffering from cancer a favorable therapeutic effect. Nevertheless, the problem is of the same type and attempts to administer tumor extracts by intradermal injections seem to augment the resistance of the organism to cancer. He cited the use of colchicine on tumors induced by the Shope virus in rabbits, in which these tumors regressed following the use of this drug and remained immune to all further inoculation of the Shope virus. Here again the immunity was specific, for these rabbits remained capable of producing another type of tumor such as tar cancers if subjected to repeated applications of tar. However, in order to produce the cures by means of colchicine toxic doses had to be used, and several animals died as a result.

Rubens Duval stressed the point that immunity is only acquired after absorption of neoplastic elements, and he concluded that the immunity was due to this resorption.

The dissemination of cancer cells in the peritoneal cavity in cases of abdominal tumors, either through the blood stream, in cases of cancers of diverse sites, is accompanied, it would definitely seem, by the destruction of a more or less considerable number of cells, probably a larger number than those which survive in the tissues where they become implanted.

He asks if this dissemination may not be an immunizing factor. "Does laparotomy,

for incomplete removal, a simple abdominal lead or even merely exploration in certain cases such as those reported by Bovier and earlier writers, where the procedure is followed by cure, temporary or definitive, act in provoking a dissemination of cancer cells, followed by their destruction and consequently an immunity? It seems that in order that immunization be acquired the organism must make the effort to destroy a certain number of intact cancer cells. The resorption of extensive neoplastic masses which have been profoundly modified by therapeutic doses of radiation does not give immunity."

One must not think, nevertheless, that the spontaneous resorption of a tumor necessarily confers immunity. One knows of cases in which the disappearance of a primary tumor has not prevented the development of metastases, and inversely, other cases in which metastases were absorbed while the primary tumor was continuing to grow.

In conclusion he pointed out that there are many unknowns in this problem. In any case it seems clear that in conditions as yet undetermined, the resorption of cancer cells is a factor of specific immunity, hence the interest in treatments which may be able to provoke this absorption and this immunity. (Rubens Duval, 1938)

In discussing/ ^{the} growth energy of malignant tumors, Rohdenburg(1918) stated:

"It can be definitely asserted that regressive changes varying from a temporary standstill to the complete disappearance of the tumor, whether it be of epithelial or connective tissue origin, may occur at any age period, in either sex, and irrespective of the location of the growth. Though no accurate data can be given for the frequency of complete regression, Bashford has estimated that it occurs once in a hundred thousand cases. . .

"The general body reactions in man during tumor recession are of several different types. The greatest number of spontaneous regressions have occurred following incomplete surgical removal of the tumor. . .during some acute febrile process, and least frequently during some profound alteration in the metabolic processes of the organism, such as extreme cachexia, artificial menopause, or the puerperium. . .

"The observation that a neoplasm may be absorbed subsequent to, or during, an acute infection, opens a most interesting field for speculation. The greater number of cases in this group have occurred after an attack of erysipelas, an observation that has led to the use of the toxins of the causative organism as a therapeutic measure. However, further observation shows that recession has also occurred after smallpox, pneumonia, malaria and acute tuberculosis. No one organism is therefore specific in causing regression. In the histories of those cases given in detail, there is a common symptom, namely high temperature, sustained without remission for several days. . . Injections of bacterial toxins, while they do give rise to violent febrile reactions, are not characterized by the continuance of fever in full violence and without remission over a period of 48 hours. . .

"It may be concluded that recession of a malignant growth can occur in either sex, at any age period, with any type of malignant tumor, and irrespective of the location of the growth. It occurs after a variety of conditions, a proof that no particular one is specific, and it is very probable that all the conditions noted are preliminary, so to speak, and act by depressing the proliferative energy of the malignant cell until the defensive forces of the body (cytotoxins, cytolytins) are able to accomplish the final destruction. It appears that the most efficacious of all the many conditions which can bring about the regressive change is heat. . . whether this heat be the result of some general acute infection such as erysipelas, tuberculosis, or pneumonia, or whether it is applied from external sources. . . That such a regression does ever occur suggests that there may be found some method of bringing it about at will. . ." (Rohdenburg, 1918)

Role of the Lymphocyte in Cancer Immunity

Murphy and Sturm (1919) reported: "Pathologists from an early date have noted that lymphocytes accumulate about the slowly growing cancers, while they are absent from the rapidly growing malignant types." These authors concluded from their experiments on the effect of stimulation of the lymphocytes by dry heat on the rate of growth of spontaneous tumors in mice that the lymphoid tissue does offer a resisting influence to cancer growth.

Summary of their experiments with spontaneous tumors: Spontaneous cancers were removed from a series of mice by operation. The animals were then subjected to an exposure of dry heat at a temperature of 55°-63° C. for five minutes. This caused a slight fall in the circulating lymphocytes, followed by a marked increase, lasting two to four weeks. Accompanying this increase of circulating leukocytes there is a marked activity on the part of the lymphoid organs as evidenced by numerous mitotic figures in the germinal centers. Immediately after heating, a graft of the original tumor was returned. The mice so treated exhibited a marked increase in their resistance to the growth of the cancer graft, over 59% remaining entirely free from a return of the cancer. In a control series in which no heat treatment was given, 96% of the animals showed a return of the cancer.

As to the effect in transplanted tumors, these authors stated "The absence of any acceptable demonstration of antibodies to explain cancer immunity suggests strongly that this type of resistance probably comes under the head of cellular immunity. The evidence connecting the lymphocyte with the resistance to transplantable cancer may be briefly summed up as follows:

- a. The presence of lymphocytes and related cells about a cancer graft in immune animals, and the relative absence of these cells around such a graft in highly susceptible animals.
- b. The general changes which take place in the cellular elements of the tissues of animals potentially immune to cancer (DaFano, 1912, pp. 57-79).
- c. The lymphocytic crisis in the circulating blood of potentially immune animals after inoculation with cancer.
- d. Destruction of potential cancer immunity by depletion of the lymphoid cells by x-rays.
- e. Destruction of established cancer immunity by depletion of the lymphoid cells by x-rays.
- f. The marked increased resistance to cancer after artificial stimulation of the lymphocytes.

"That other factors than the lymphocytes are involved in the process of cancer

immunity seems more than probable. . . (but) we have in the lymphoid elements an important link in the process of so-called cancer immunity."

Summary: "The marked and durable stimulation of the lymphoid elements induced by dry heat applied to the animals results in the establishment of a high degree of immunity to certain transplantable cancers in mice." (Murphy and Sturm, 1919)

X-ray Effects on Cancer Immunity

Russ et al. (1919) reported on their experimental work on the effects of small doses of x-rays on the blood of rats and on the susceptibility of these rats to transplants of Jensen's rat sarcoma.

They stated: "An attempt is made to show the possible bearing of the salient features of these newly acquired facts upon the present day treatment of malignant diseases by means of x-ray. It will be generally admitted that in such treatment attention is usually focussed upon giving the malignant cells a lethal dose of radiation."

They enumerated the salient experimental findings of their own group as well as Murphy and his group at Rockefeller Institute, as follows:

1. The natural immunity which animals usually have towards the inoculation of spontaneous tumors can be broken down by an x-ray exposure sufficient to cause the disappearance of the lymphocytes (Murphy and Morton, 1915).

2. The acquired immunity which results from the inoculation of blood or other cells into normal animals can similarly be destroyed (Murphy & Taylor, 1918, p. 1).

3. The acquired immunity which is found in animals in which tumors have disappeared can likewise be broken down (Mottram & Russ, 1917).

4. Heterologous tumor transplants which usually grow only with great rarity, multiply rapidly in an x-rayed animal, until such time as the depleted lymphoid system is well advanced in regeneration (Murphy, 1914, p. 1459).

5. Acquired immunity is destroyed only so long as lymphoid cells are reduced in number (Mottram & Russ, 1917).

6. In contrast to these actions, an immune condition can be produced instead of destroyed by suitable doses of x-rays: small daily doses, 12 seconds each day

for two months, Coolidge tube, worked by induction coil at an alternative spark gap of about 4 inches (4 cm. between spheres, 5 cm. diameter); no screen was used other than a thin sheet of mica covering the x-ray tube box and a thin perforated sheet of celluloid covering the box in which the animals were placed. The distance between the anode and the animal was 30 cm., i.e., medium or medium soft rays were given. They noted that Murphy and Morton (1915) had obtained a similar effect upon mice bearing spontaneous tumors. They concluded therefore that x-rays administered to an animal have two effects, quite apart from their direct effect upon a tumor:

- (a) a large dose by destroying the immune condition will favor the growth of a tumor;
- (b) a small dose, by producing the immune condition, will help to control and overcome the growth of the tumor. They added:

"The bearing of these facts upon the radiological treatment of malignant disease in man appears to us to be as follows: Whenever a tumor is exposed to x-rays the lymphocytes circulating in the blood vessels of the growth and of the surrounding tissues will be irradiated, or if the site of operation be treated, the lymphocytes in the normal vessels and tissues will be similarly exposed. It is clear therefore that though the radiologist may be giving the primary growth the dose of radiation required for its disappearance, he may at the same time be indirectly encouraging the development of secondary growths by lowering the natural powers of resistance of the patient, especially if this comparatively large dose is repeated at fortnightly intervals, as in post-operative treatment.

"It would appear profitable therefore to take all possible precautions to prevent the destruction of such cells as the lymphocytes, which, there is good reason to believe, play a defensive role in many varieties of malignant growth."

They believed that there was "a distinct analogy between a graft introduced experimentally and a lodgement of cancer cells occurring at a distance from a primary growth. By the use of small doses of x-rays repeated at intervals it may be that the resistance against the development of secondary deposits can be increased in a similar way to that which occurs in the case of an experimental inoculation."

They mentioned that "these and other researches were the outcome of a line of investigation which had its origin in the basic fact that x-rays cause carcinoma

(Lancet, June 26, 1909. Croonian Lectures on Radio-activity and carcinoma, Royal College of Physicians). (Russ, Chambers, Scott & Mottram, 1919)

Effect of X-ray and Ultra-Violet Rays upon Lymphocytes

H.D. Taylor (1919) stated: "Experiments reported previously indicate that in animals a blood lymphocytosis attends increased resistance to cancer and tuberculosis. The work has shown that the number of circulating lymphocytes can be varied by suitable dosage of the Roentgen rays. Massive x-ray exposures decrease, while small ones increase both proportionately and actually, the number of lymphocytes in the circulating blood."

He therefore studied the effects of solar rays in the temperate zone in mid-summer and found that they do bring about changes in the white blood corpuscles of blood similar to that recognized as characteristic of small doses of x-rays. Because of the parallelism between the tanning and the blood changes it seemed probable that the lymphocytosis observed in the majority of instances, which is similar to the response of the blood to smaller doses of the x-rays, is due to the ultra-violet rays contained in the solar spectrum. (H.D. Taylor, 1919)

Radiation and the Lymphocyte

Nakahara (1919) studied the changes in the lymphoid organs of rabbits following small doses of x-rays.

The nature of the lymphocytosis induced by heat and of that produced by x-rays is indistinguishable, since the lymphocytic changes are exactly parallel in both cases, i.e., always with a characteristic fall preceding the marked rise. However, he noted that the experiments he described had shown conclusively that the lymphocytosis produced by the small doses of x-rays was due to a primary stimulative effect of the agent and hence was different from the similar lymphocytic change induced by heat which was "a sort of regeneration" phenomenon.

Throughout the experiments there was no indication that the dose of x-ray used was injurious to any of the lymphoid tissues examined. Mitotic figures were seen to become gradually more abundant after the treatment. In the spleen this enhanced pro-

liferative activity of the cell reached its height four days after the treatment. In the lymph nodes this stimulative change was distinctly manifested earlier and was more extensive than in the spleen. These histologic findings were in harmony with the results of the blood counts which showed the increase of lymphocytes became most pronounced about one week after treatment and persisted in a slight degree up to the 14th day.

He concluded that the lymphocytosis so induced was due to a primary stimulative effect upon the lymphoid tissue of the animal. (Nakahara, 1919: cited by Murphy, 1926)

Lymphoid Activity and Tumor Immunity

Murphy, Nakahara and Sturm (1921) felt it would be of importance to know whether there was a difference in the resistance percentage when the tumor inoculation was made at varying times after the stimulus was produced, i.e., the relation between the time and extent of lymphoid stimulation induced by physical agents and the degree of resistance to cancer produced in mice.

They found that the small dose of x-rays used (spark gap 3/8 inch, milliamperage 25, distance 8 inches, time 10 minutes) gave a sluggish lymphoid cell reaction of short duration with a definite latent period between the treatment and the evidence of marked stimulation, while after heat (cage 55°C. for 5 minutes, temperature rarely rising to 63°C.), a short period of depression is followed by a sharp stimulation over a much longer period. The cancer inoculation made at the height of the stimulation phase shows a definite increase in the immunity. Animals inoculated with cancer immediately after the heat treatment exhibited a pronounced immunity, but not so marked as that shown when the inoculation is made at the height of the stimulation.

The amount of resistance shown when the cancer inoculation is made at the height of the moderately stimulating effect following exposure to x-rays is much less than that seen when the inoculation is made at the height of the heat effect when the stimulation is much greater. When the lymphocytosis sets in after the cancer graft is established only a slight effect is noted. All these results indicated that the degree of immunity is dependent on the amount of lymphoid stimulation existing either

at the time of or following soon after the cancer inoculation. (Murphy, Nakahara, Sturm, 1921a)

X-ray Effects on Immunity

Nakahara and Murphy (1921), in studying the effect of small doses of x-rays of low penetration on the resistance of mice to transplanted cancer, concluded that if cancer inoculation is made immediately after the stimulative treatment with x-rays, no lymphoid stimulation occurs such as would occur if the cancer inoculation were not made. But if the cancer inoculation is made seven days after the x-rays are given, thus allowing the stimulation to develop before the inoculation, there is in the majority of cases what might be called a second stimulation of lymphoid tissue.

They noted the parallelism between the lymphoid reaction accompanying the immunity to cancer grafts induced by physical agents (x-rays) and that induced by a biological agent (homologous blood). They had already shown that mice immunized to cancer by means of an injection of defibrinated blood showed an increase in the number of mitotic figures in the lymphoid tissue. Such mice when inoculated with a cancer graft 10 days later exhibit a second stimulation of the tissue, as well as a marked blood lymphocytosis. The experiments reported showed a corresponding effect brought about by small doses of x-rays. Only the animals showing an increase in the lymphocytes proved to be resistant to cancer. This state of resistance to cancer inoculation was attended by blood lymphocytosis as in the case of all other varieties of immunity to transplanted cancer thus far studied. (Nakahara and Sturm, 1921; cited by Nakahara, 1922, as showing that by stimulation of the proliferative activity of the lymphoid cells with certain physical agents one can increase the resistance to cancer implants)

X-ray Effect on Immunity

Liu, Sturm and Murphy (1922) showed that small doses of x-rays can be made to induce a local change in the subcutaneous tissue similar to that which it produces in the skin. This change in both instances renders the locality resistant to the

growth of implanted cancer cells, but does not affect the general resistance of the animal. The authors stated: "This is an additional point to be taken into consideration in determining the method of treatment and the interpretation of results following the use of x-rays as a therapeutic agent. The clinician has rarely taken into account other possibilities than the direct destruction of the cancer cells.

"X-rays under certain conditions materially increase the general resistance of the body to cancer, an observation made in this laboratory, and later confirmed by Russ, Mottram and their co-workers. On the other hand, excessive doses of x-rays are capable of lowering both natural and induced resistance to cancer. The amount required to kill mouse cells is many times that which can be tolerated by the skin, yet as shown above, a mild erythema dose is sufficient to render the skin, and under proper conditions, the subcutaneous tissue, antagonistic to the growth of implanted cancer. It is undetermined which of these various qualities are responsible for the successes and failures in the treatment of human cancer. It would seem of prime importance to estimate the relative value of these effects, for it is not beyond the possible that a method of treatment could be devised which would make use of the favorable and eliminate the unfavorable action of this agent."

Tumor Immunity Induced by X-rays

Murphy, Maisin and Sturm (1923) studied local resistance to spontaneous mouse cancer induced by x-rays and concluded: "It is evident from our experiments that, as far as mouse cancer is concerned, the beneficial result from x-ray therapy is due to the reaction in the normal tissues induced by the rays, not to any direct effect on the cancer cells. That this point first brought out with a transplantable tumor, and now confirmed for the spontaneous disease, may hold true for human cancer, is not improbable. Statements by Ewing (1922) based on a careful study of human material, indicate that the reaction induced in the surrounding normal tissues by x-rays or radium is of as great importance as we have shown it to be in animals. In a recent address he makes the following statements: 'It is clear that the reaction of the tissues is an essential factor in the curative process. Under some circumstances,

when this reaction fails, no amount of radiation succeeds in killing the tumor cells . . . The most detailed knowledge we possess indicates clearly that the curative action is not the result of a direct effect exclusively upon the tumor cells, but involves especially the peculiar reaction of the normal or invaded tissues".

Murphy et al., in summarizing their own experiments, stated: "Autografts from a spontaneous tumor of mice when replanted into areas previously exposed to an erythema dose of x-rays, failed to grow in the majority of instances (71.4%), while similar grafts inoculated into untreated areas grew in a large proportion of cases (83.6%).

"Autografts of spontaneous cancer established and growing in the skin disappeared in 76% of animals after the tumor and surrounding tissues had been exposed to an erythema dose of x-rays, whereas other autografts of similar derivation that had been given a like dose of x-rays outside the body and had been implanted in the same animals grew progressively in 90% of instances. That this result was not due to a greater susceptibility of the cancer cells x-rayed in situ was shown by the fact that tumors treated in situ with x-rays and then replanted in an unrayed location on the same animal grew actively. Evidently the ray had done no direct damage to the cancer cells." (Murphy, Maisin & Sturm, 1923; See below, Goldfelder, 1942, for further studies of different effects of x-ray dosage used on conferring or destroying immunity to tumors).

Inflammation. Studies on Lymphoid Activity

Nakahara (1922) studied the effects of injections of olive oil in producing immunity to transplanted cancer in mice. He stated:

"It has frequently been suggested that the lymphoid cells are in some way concerned with the absorption and digestion of fats and liquids. Recently a number of investigators have reported on the cellular changes following injections of these substances. Ramond (1904) found that olive oil injected intraperitoneally is gradually absorbed by the white cells of the lymphoid variety, and Clark (1917) noted that the subcutaneous injection of olive oil exerts what he considers to be a chemotactic influence on the lymphatic endothelium and lymphocytes. Bergel (1919, 1920,

1921) confirmed and extended these observations by finding that the cellular exudate after an intrapleural or intraperitoneal injection of fatty oil or oil emulsion in animals is almost entirely made up of the lymphoid type of cell.

"It is well known that the local reaction following an injection of homologous living tissue in mice consists mainly of a lymphoid cell outpouring similar to that described above. Murphy and Nakahara observed that this local reaction is accompanied by evidences of increased proliferative activity among the lymphoblastic cells of the spleen and lymph nodes. Mice thus injected with homologous tissue become highly resistant to transplanted cancer. A like stimulation of the proliferative activity of the lymphoid cells may be induced by certain physical agents with resultant increased resistance to cancer transplants.

"In view of these observations, it was regarded as of interest to determine whether or not the local reaction to oil is accompanied by a general lymphoid stimulation and, if so, the effect on the resistance to cancer inoculation in mice."

These experiments demonstrate that resistance to cancer may be induced by the intraperitoneal inoculation of a suitable quantity of olive oil. Thus resistance can be induced by three classes of agents: homologous tissue (biological); x-rays and dry heat (physical); and olive oil (chemical).

The associated manifestations are the same for all three: a latent period after the treatment when there is no evidence of resistance. The maximum degree of resistance appears at about the 10th day. This state of resistance is preceded by a proliferation of the cells of the lymphoid germ centers and after inoculation is associated with a local cellular reaction (lymphoid infiltration) about the cancer graft as well as by a second stimulation of the lymphoid germ centers, an increase in the number of circulating lymphocytes, and a marked increase in the proliferative activity of the lymphoid organs. The indirect evidence associating the lymphoid cell with the mechanism of resistance to cancer is so strong as to leave little doubt that this cell has an important, if not the most important, role in bringing about the resistant state.

Nakahara (1924) stated: "The possibility that the cancer immunity induced by unsaturated fatty acids may be consequent on increased activity of the lymphoid tissue deserves consideration. The close relationship between fat metabolism and the lymphoid tissue, under both physiological and pathological conditions, and the clearly demonstrated association of lymphoid stimulation with cancer immunity, are in favor of this view." He had noted that injections of sodium oleate in amounts sufficient to produce immunity also bring about a marked increase in the number of karyokinetic figures in the lymphoid tissues, indicating an increased proliferative activity of this tissue.

In 1926 Murphy summarized all the investigations which had been done by his group (Nakahara, Sturm, Liu, etc.) at the Rockefeller Institute in the preceeding 14 years on the role of "The lymphocyte in resistance to tissue grafting, malignant disease and tuberculous infection". The studies thus assembled had previously appeared in over 60 publications. They were published as Monograph No. 21 by the Rockefeller Institute for Medical Research, 1926. This deserves to be studied at the present time in the light of more recent investigations as regards the importance of lymphoid activity and the inflammatory reaction in host resistance to cancer.

Tissue Resistance to Malignant Disease

Boyd (1921), in discussing tissue resistance to neoplasms, noted that many of the peculiarities of distribution of metastases can be explained on anatomical grounds. It is easy to see why the liver should be so frequently involved in neoplasms of the alimentary tract, the lungs in those of the uterus. Although tumor cells must be carried in large numbers to the heart, the spleen and the muscles, yet metastases in the two former are rare and in the latter almost unknown. Is this because the heart and the spleen are pulsating constantly and the muscles are also active? Muscles also provide a highly acid environment and cancer cells prefer an alkaline environment. Boyd believed that there probably exists "a preliminary interval during which it is not possible for secondary growths to be set up, a refractory period in which the

tissues are being sensitized and prepared, it may be by the action of ferments produced by the tumor cells--a period. . .of comparative immunity."

He then cited three cases illustrating some points in tissue immunity:

CASE 1: Mrs. M., aged 40, a stout, well-nourished woman; developed scirrhus carcinoma of the breast in the fall of 1915, with axillary node involvement confirmed by microscopic examination; the breast was removed. Early the next year metastasis developed in the right humerus. By Septmeber 1916, there was extensive involvement of the right humerus, right femur and pelvis. In October 1917, she was bedridden, unable to feed herself, with spontaneous fractures of both humeri and numerous firm nodules over the vault of the skull. Numerous x-rays showed involvement of skeleton of most remarkable extent. It almost appeared as if not a bone in the body had been spared--skull, humerus, radius, ulna, femur, tibia and fibula on both sides, pelvis, small bones of the hands and feet. Arrangements were made for the patient to be sent to a home for incurables, but in the four months' delay prior to getting her in, "the clinical picture underwent a most extraordinary transformation. The nodules in the head disappeared, the fractures of the arms united, strength returned to her legs, she was able to sit up and knit, and by the time she left she could walk almost without assistance. Boyd stated: "Such an outcome is not rare in slowly growing primary tumors in old people, and the failure of metastases to form owing to the unsuitability of the environment is an everyday occurrence. The disappearance, however, of metastases so widespread as to involve almost every bone of the body, and so far advanced that spontaneous fractures had occurred is a phenomenon as startling as it is incomprehensible. It proves beyond cavil that the body may acquire at least for a time an immunity to malignant disease."

CASE 2: Mr. W., aged 71, had always enjoyed good health until 1913. In that year a pigmented warty growth developed on the plantar surface of the heel. It was removed, found to be a malignant melanoma, and soon recurred in the margin of the scar. It continued to grow and was removed again in 1916 but soon recurred. In 1917 the nodes in the groin became enlarged and continued to increase in size until they formed a pigmented mass the size of a fist. The primary growth was removed for the third

and last time in 1918. At the end of 1919 pigmented spots began to appear on the leg between the knee and the ankle. There were raised, firm nodules about $1\frac{1}{2}$ cm. in diameter, some of an intense jet black, others showing little spots of black here and there on the surface. A few months later small pigmented spots appeared on the chest wall and the side of the nose. By August 1920 the leg presented a most classical picture of malignant melanoma. There was also a huge pigmented mass in the groin, marked collateral circulation in the abdominal wall suggesting pressure on the inferior vena cava. A spontaneous fracture of the rib had occurred in July 1920, and was possibly due to involvement of bone. In reporting this case Boyd stressed the fact that during the seven years that the patient had suffered from malignant melanoma, for six he had been in perfect health and vigor, able to do a full day's work. Only in the last year had he not felt strong enough to work and had finally been confined to bed for two months. He added: "Such a patient must have a wonderfully high relative immunity which is only now breaking down."

"At the same time, the general conception of the malignancy of melanomata is unduly gloomy. As Sampson Handley puts it, the prognosis had been painted in tones as black as the characteristic nodules. It is true that dissemination is terribly rapid in many cases and death may follow in a few months. In others, however, tissue immunity is sufficient to allow of successful operative interference.

"Very rarely the reaction on the part of the tissues is sufficient temporarily, at least, to destroy the secondary growths." Such a case is that reported by Pearce Gould and referred to by Handley in his Hunterian lecture on melanomata: a small congenital mole was removed from the chest, after it had been growing larger for three months. Removal was soon followed by the appearance of tumor nodules in and under the skin. When first seen by Pearce Gould nine months later, the nodules were scattered over the greater portion of the body. A month later it was found that no new nodules had appeared, and that most of these already present were very much smaller. So were the enlarged lymph nodes. In the course of a few weeks all the nodules had disappeared with the exception of two small ones. The patient gained considerable weight. Six months later cutaneous nodules again appeared, and the pa-

tient soon died after being confined to bed only three or four days.

CASE 3: Mr. P., a healthy farmer aged 38, was first seen in March 1918, with a mass in the right axilla, of nine months' duration. Seven years previously he had had a growth of unknown nature removed from the interscapular region. "It had troubled him so little that he did not leave his work to come into the city to be treated." It was removed and proved to be a typical malignant melanoma, containing a large amount of pigment. He made a rapid recovery and did a full summer's work on the farm. In the fall several blackish nodules appeared on the skin of the chest and anterior abdominal wall. These were excised and proved to be identical in microscopic structure. The health remained unimpaired, but realizing the seriousness of his condition, he insured his life as a first class risk.

In June 1919 he reappeared suffering from an acute abdominal condition which proved to be an intersusception. At operation an enlarged lymph node was found close to the intersusception which probably had caused it. Sections showed melanoma. In September 1919 he again presented himself complaining of sore throat. It was found that the tonsils were converted into two large black masses which were removed with perfect ease, also proved microscopically. He returned to his farm and continued to work throughout the winter, but in the spring he succumbed rather suddenly. He thus enjoyed nearly three years of robust health after metastases developed, 10 years after the onset of the growth in the interscapular region.

"The fate of a metastasis depends not only on the proliferative activity of the tumor cells, but also upon the behavior of the tissue in which they are implanted."

Boyd noted that Murphy and his co-workers were of the opinion that the essential immunity mechanism against carcinoma is the proliferation of lymphocytes so frequently seen in the neighborhood of a malignant growth.

"He has shown experimentally not only that a strong dose of x-rays, by injuring the lymphoid tissue of the body, may render the animal more susceptible to the inoculation of tumor fragments, but also that by stimulating the lymphoid tissue by a small dose of x-rays the animal may be made correspondingly immune." (Boyd, 1921)

Vaughan and Eppler (1923) described experiments which demonstrated quite conclusively why cancer is so difficult to cure when once established, as well as why one case succumbs rapidly to the disease, while in another it progresses but slowly.

They concluded: "Whether recurrence be rapid or slow after surgical removal of cancerous lesions, where all tumor tissue has not been removed, is dependent not upon the type of operation performed but upon the patient's own ability to form antibodies antagonistic to the growth of cancer cells." This ability is evidenced by the percentage of mononuclear cells present in the circulating blood stream. When a high percentage of large mononuclear cells is noted for several days in succession, the tumor retrogresses during that period. Conversely, when the count shows a high percentage of polymorphonuclear cells over a considerable number of days, it signifies rapid tumor growth.

These antibodies that destroy cancer cells are extremely unstable, they last only a matter of a few hours--very different from say the immunity produced with the typhoid bacillus, which may last a lifetime.

"For this reason the term transitory immunity has been used to distinguish that particular type, lasting but 4 to 24 hours, that is elicited when cancer tissue is injected into a healthy animal. Quite obviously it is the the explanation of why the body so seldom rids itself of cancer, since if substances are formed which destroy cancer cells and such substances are lost before their work is completed, the tumor is given opportunities to grow again before new antibodies are formed.

"That some people suffering from cancer are better able to form antibodies than others explains why cancer grows and forms metastases rapidly in some individuals but slowly in others. Rapid recurrence and death in cancer is not dependent so much upon the type of treatment employed as upon the ability of the person afflicted to form substances which inhibit the growth of cancer cells. That this is actually the case can be proven by running a long series of blood counts on cases progressing both well and poorly.

"Metastasis does not occur until the immune mechanism has been destroyed and is no longer capable of being stimulated to renewed function. The injection of cancer

protein or of a vaccine or residue prepared from any tissue that normally produces a decided increase in lymphocytes is a useful method of ascertaining the presence or absence of metastasis, since subsequent blood counts will demonstrate the ability of immune bodies to be formed. Occasionally, even with metastasis, the body will manufacture immune substances over a considerable period. It is such advanced cases that appear to cure themselves and in which the physicians should be guarded in making a prognosis as to length of life. Such patients frequently live months after death has been predicted and furnish a fruitful field for the charlatan, since the temporary benefit observed from Nature's efforts is frequently credited to whatever medication is being used at the time."

Importance of Stroma in Cancer

Durante (1923) cited the paper by Dupont and Leroux in which they reported that in cancers that are treated by irradiation, a favorable clinical course coincides with an active stroma reaction, and in cases of rapid recurrence, this coincides with absence of this defense reaction of the stroma.

Durante stated: "The attention of histologists has until now perhaps been confined too exclusively upon the neoplastic cell. We have always accorded a great importance to the reactions of the stroma, whether inside the neoplasm or in its immediate periphery, and we have insisted since 1920 on the interest which these reactions may present as regards pathogenesis, development and even treatment of tumors." (He had begun these studies prior to 1914, when they were interrupted by World War I.) He cited the interesting report of Rubens Duval (1914) on this question and noted that Roussy had become interested and had encouraged some of his collaborators. Thus the development of cancer involved two factors: 1. The activity of the epithelial proliferation, which is rather clearly indicated by the morphology of its elements. The more rapid the growth, the less differentiated and more embryonal the cells. 2. The second factor is the reaction of the stroma, more difficult to interpret.

Most frequently one encounters inflammatory reactions, more or less localized

or diffuse, and sometimes several types coexist in different portions of the same neoplasm..

Before being able to estimate the importance of this reaction on the course of the tumor, it is important to determine its cause.

It may be present prior to onset of the tumor and may represent only the prolonged irritation which finally ended in a malignant degeneration. (Interesting from an etiological standpoint, but since it indicates the persistence of a determining cause, this would be unfavorable as regards prognosis.)

It may be secondary to the onset of the neoplasm, indicating a real effort of the organism against the invading parasite which the neoplastic elements represent.

It may be due to an accidental complication such as infection in the ulcerated tumor or therapeutic intervention. The latter is usually easy to recognize, but the first two are difficult to evaluate as regards prognosis.

The greater intensity of the reaction in the immediate vicinity of the invasive cancer nodules appears to be an argument in favor of a defensive local reaction against malignant invasion. In cases of diverse reactions in a simple tumor, it is at the periphery that one must especially attribute the evidence of defense.

Such as they are, these diverse reactions of the stroma are capable of modifying, more or less, the epithelial evolution, especially when they are intense and generalized throughout the neoplasm.

When there is a very intense reaction, stimulating the defensive forces of the stroma may enable it to battle victoriously against the invader, and a very acute infection (erysipelas) has sometimes produced cure.

A subacute or generalized reaction even though it may moderate slightly the course does not seem to present a serious obstacle to the evolution of the neoplasm.

The chronic form always produces a considerable slowing down of the growth.

Retractile sclerosis is an effective reaction. It stifles and destroys the neoplastic elements, but it must extend over the entire neoplasm in order to produce a real cure. One seeks to provoke it, ^{and} it may exceptionally occur spontaneously. Also, we know that the awakening of the defense mechanisms of the connective tissue

may result in a cure.

Whatever may be the point of departure of the modifications of the stroma, the two extreme forms, the acute and the sclerotic, seem to be the only ones able to exert an effective force against the neoplastic element. It is necessary to try to produce them therapeutically.

Thus, chemical cauterizations have been used and infections have been induced. In any case, these methods only applicable to certain easily accessible organs run the risk in cases of failure of stimulating the neoplastic elements and of inducing an increased growth. Reverdin had advised very extensive cauterization for inoperable uterine cancers, which occasionally gave a long survival and Durante observed the hardness and thickness of the cicatrices obtained by Keating Hart with fulguration. His own experiences attempted to obtain at a distance a progressive sclerosis of the stroma without proceeding to the acute form of reaction.

We do not yet know the exact mode of action of x-ray or radium. They appear to act not only upon the neoplastic cells, and the studies of Dupont and Leroux seem to indicate that they are capable of stimulating the stroma and of developing means of defense. (Durante, 1923)

Tumor Immunity

Des Ligneris (1935) stated that "therapeutic measures directed against any disease act by making use of the already present, though often quantitatively insufficient methods, which nature sets up against the disease. In the case of cancer, there is a distinct indication that the cancer-bearing organism tries, though in vain, by the production of immune bodies to protect itself against the growing tumors. All the methods which by general action occasionally arrest growth do so probably by increasing through non-specific stimulation, the specific anti-action of the organism.

. . . "I am inclined to think that the success with Dr. Cornell's method (ensol) may occasionally be brought about by a non-specific stimulating of the naturally present, though quite insufficient, specific anti-action of the organism. But. . . this action is uncertain and insufficient in the majority of cases. . . " (Des Ligneris, 1935)

Woglom (1929) made an exhaustive review of immunity to transplantable tumors, in which he discussed some 600 papers, most of them published between 1913 and 1929. The previous literature had been summarized in his book, "A study of experimental cancer," 1913.

He emphasized the need for more extensive experiments involving hundreds of mice before authors published results that would be seriously considered, also the importance of using a pure breed of mice.

Natural Immunity:

"That adult animals of a foreign species enjoy complete immunity to the continued proliferation of a subcutaneous graft is disputed by but a few writers, later work upholding the results of the earlier investigators. . .

"Murphy believed 'the small round cell to be a factor of prime importance in species resistance, since it was absent in susceptible tissue such as the embryo and the brain. In this explanation Hardy concurred, having found the lymphocytic response in the brain much less active than in the subcutaneous tissues or the muscles, while Maisin and Sturm could discover no reaction of any sort in this organ, unless the graft happened to come in contact with the wall of the ventricle; in such cases . . . an intense lymphocytic reaction developed and the graft failed.'"

Mouse and rat tumors can be grown in vitro in the plasma of all alien species investigated except in that of the goat.

Heredity:

It is the general opinion that natural immunity is hereditary.

Local Influences:

"There can be no doubt that extraneous factors in both host and graft may affect the outcome of inoculation. In the host there have to be considered such influences as inflammation, anemia, or hyperemia; in the graft the proportion of necrosis, age of the tumor which it is taken, etc.

"According to Vlès and de Coulon, the injection of substances which cause a variation in the iso-electric point of the host's tissues towards high pH values increased susceptibility, and vice versa, though the reaction is not a specific one.

"....Russell, Bashford, Tyzzer and Murphy and Lewin have all suggested that natural immunity is only the power to react promptly with a defensive mechanism to choke off the graft before it obtains a foothold. Mottram and Russ shared this opinion, pointing out that natural immunity to the Jensen rat sarcoma appeared to be acquired during the regression of a small nodule, for they had never seen in normal rats the complete inhibition of proliferation observed in immune animals. Uhlenhuth and Seiffert concluded that immunity, whether natural or produced by tumor, or by normal tissue, seemed to be the same; the differences were quantitative only. (p. 146)

Acquired Immunity:

"Of the homologous tissues, embryo skin is still acknowledged to be the most efficient." (p. 147). Bashford found that practically all the organs and tissues would immunize, though for technical reasons some were preferable to others. Spleen, while unusually efficient, was apt to be infected, as was liver, which in any case was not so active as spleen.

As with other antigens adequate amounts are required: 0.3 to 0.5 cc. of blood, 0.05 cc. of fixed tissues. The immunizing power of the blood appeared to reside in the white cells, both the granular leukocytes and the lymphocytes being active.

The majority of investigators believed that tissue will produce immunity only when living; but Caspari (1929) and his associates believed that its death was the essential feature. Necrotic material (necrohormones or chemical substances elaborated in dying cells) caused formation of stroma and a capsule, nourished the tumor cells, exerted a toxic effect and called forth a general immunity. Immunity was not so active when necrosis took place outside the body. Caspari and Ascoli concluded that the ability of tumors to immunize was greater the high their growth energy.

Bullock and Rohdenburg (1920) could find no evidence that immunity was solely the result of either the life or death of the injected tissue.

Haaland demonstrated (1909-1910) that devitalization of normal or of cancer cells by radium or certain other agents robbed them of their immunizing power.

Contamin (1910) found that if the dose of x-ray was mild, immunizing power was retained. These findings were confirmed by Wedd, Morton and Russ, Lepper, Mottram, and Chambers. "Their general impression was that the agent causing resistance was produced by the tumor cell during death after irradiation and that any treatment which caused immediate destruction prevented elaboration of the effective agent."

Later Chambers and Scott repeated the view that the agent causing immunity to the Jensen rat sarcoma is a product of the dying tumor cell, but said that the difficulty of detecting and isolating it was increased by the fact that the breaking down of the cell was accompanied by liberation of a second substance, which stimulated tumor growth.

Tizzoni, Centanni and DeAngelis found that Ehrlich adenocarcinoma was completely absorbed after mice bearing it were treated with tumor exposed to 24 hours of radium, but 48 hours of radiation deprived the cells of all curative power.

Woglom then cited the studies of Chambers, Scott, Russ and Kellock in attempting to immunize patients against their own neoplasms. They regarded the procedure as devoid of danger since the amount of radiation employed was such as to retain immunizing activity while abolishing growth power. Twelve cases were treated, five of them died, the remainder being in more or less good health up to 14 months later, when the paper was published.

Wood and Prigosen used 6000 animals, testing resistance with an "unusually energetic neoplasm", mouse sarcoma 180, or with Flexling-Jobling carcinoma, rat carcinoma 10, or mouse carcinoma 11. They found that irradiated tissues neither protected against inoculation nor retarded progress of grafts already established.

Caspari also discussed the perils of treatment with devitalized tumor because even extraordinarily large doses of radiation may not suffice to kill all the cells.

In a discussion between Wood, Chambers and Russ regarding this method, Wood pointed out that the inoculation of radiated material in humans was said to have been followed in England on at least one occasion by extensive metastasis.

The injection of patients with their own emulsified and treated tumors was reported by Von Dungern to produce edema and reddening, whereas neoplasms from

other persons were inactive, a hypersusceptibility which he regarded as of surprising specificity.

Woglom was not impressed with the studies of Rondoni (1912), Kepinow or Takahashi (1922), who inoculated fragments of heated or boiled tumor tissue to produce immunity. Most of these observers used too few animals or did not mention the number of animals.

Woglom stated that "the only experiments in this field that possess any interest at all are those of Koenigsfeld (1913-1915) which really deserve repetition. He used Pohl's rapid method, smearing the tissues on a glass plate and drying them in a vacuum at room temperature. After 24 hours, the material was scraped off in a fine powder ($\frac{1}{4}$ - $\frac{1}{5}$ the weight of fresh tissues). Tumor dried this way and suspended in water did not grow after inoculation but conferred resistance when administered intensively in increasing amounts. The immunity which lasted several weeks either entirely prevented the taking of grafts, or at least restrained considerably the growth of those that did succeed in developing. The controls received dried normal tissues which conferred no immunity at all. Koenigsfeld suggested that the resistance elicited was probably specific and due to the formation of a real antibody, the number of animals employed appeared adequate."

Woglom suggested that there was a possibility that sepsis played a part in Koenigsfeld's experiments. Tissue spread out on glass plates for drying would almost certainly become contaminated in 24 hours, and this objection was strengthened by the fact that many of the treated animals died.

Nakahara recorded a distinct resistance after preliminary treatment with fatty acids; the details of this work may be found in Murphy's monograph (1926).

Concomitance:

Concomitant immunity - the resistance induced by a tumor during its growth. Some tumors possessed this immunizing power - others did not. As a rule the tumors which immunized the host were those most liable to spontaneous cure.

Distribution:

Immunity, in whatsoever way initiated, appears to spread over most of the body.

First Appearance:

The shortest length of time after which immunity appeared was four days, and it persisted for six months or more, according to Tsurumi (1915-1916) and Raposo; the time and rate of development were practically the same for sarcoma and carcinoma.

Transfer:

Immunity apparently cannot be passively acquired. The only writer to report even a trace of passive immunity was Tyzzer (1916). In the hope of disclosing evidence too slight to be discovered in the gross measurement of tumors as ordinarily practiced, he injected mice with the serum of immune mice just prior to tumor inoculation. Microscopic examination of grafts removed at various intervals showed that the serum had made the implants positively chemotactic to polymorphonuclear leucocytes, and that there was an increase in the amount of collagen within the grafts, as well as a more pronounced degeneration of the tumor cells. The implanted fragments had thus encountered in the serum-treated animals conditions which, although transitory and insufficient to produce passive immunity, were nevertheless definitely unfavorable to the growth.

Nature of Immunity:

Among the first to discuss the possible identity of immunity to transplantable neoplasms with that against normal cells was Rous. He found that mice refractory to the growth of embryo were apt to be hostile to a tumor graft as well, and that as with tumors no supporting stroma was elaborated.

Toward a fowl tumor Rous found two varieties of resistance: one against the implanted cells as such and one against the etiological agent.

The tumor problem in brief is a tissue problem, resistance being directed against the tumor graft as strange tissue merely, and not connected with any neoplastic qualities which the graft happened to possess.

Antibodies:

Although some tangible basis for immunity, something of the nature of a specific antibody had been sought for 30 years, none had yet been discovered, though the methods employed had nothing to be desired in the way of completeness or ingenuity....

"The ground has recently been gone over again with the greatest care by Lumsden (who found that)...antisera can be produced in any animal by treatment with heterologous tumor, and these contain an antibody toxic in vitro to malignant cells. Yet in vivo they are comparatively ineffectual, perhaps because they do not meet the cancer cell in sufficient concentration."

The truth is that the tumor immunizes against itself so that even rats in which it is growing are refractory to a second inoculation.

An analogy between bacterial immunity and resistance to transplantable tumors has nevertheless been several times suggested, as when Daels (1910) found that infection with *Spirillum duttoni* seemed to protect mice to a certain degree against the Jensen mouse carcinoma. Resistance seemed highest when antibodies were in the blood and phagocytes which had fought the *Spirillum* infection were also present.

Levin (1913) believed that immunity to transplantable tumors is similar to that exerted against bacterial diseases, though not identical, while Pearce and Rivers discovered that rabbits, immune to a certain virus, were more resistant to the growth of the rabbit tumor than normal ones, though the exemption was not specific.

It is well known that tumors grow poorly in animals that are not in good health, and Woglom stated that "it is reasonable to ask whether this may not be because their whole immunizing process has been thrown into a more labile state by some infectious process".

Metabolism:

Accelerated lipoclastic activity in the serum, not specific, however, to cancer, has been suggested as a possible protective process by Shaw-Mackenzie.

Uhlenhuth and Seiffert (1925) have also offered a change in the general metabolism, combined with some alteration in the reticulo-endothelial system, in elucidation of natural immunity.

INFLUENCE OF VARIOUS ORGANS:

Lymphoid System:

The lymphocyte hypothesis appeared first, perhaps, in a paper on the infective sarcoma of the dog, in which it was reported by Wade (1908) that grafts deposited in

animals that had recovered from the tumor were flooded almost at once with cells of the lymphocyte group. Lymphocytes and polyblasts were seen, also, around receding tumors, and final disappearance was associated with a flooding of the implant by lymphocytes, polyblasts and plasma cells, the nodule being finally "borne away", as Wade put it, "on a lymphocyte tide." It was suggested that recession and immunity were a product of the cytolysis of tumor cells, this being brought about in all probability by lymphocytes and polyblasts.

In the case of the more authentic tumors of the mouse and rat, the significance of the lymphocyte was first investigated by Da Fano (1910-1912). According to his description, lymphocytes gathered in large numbers around any tissue capable of eliciting immunity, and he thought that the intimate connection of these cells with the immune process might be regarded as practically certain. The plasma cell seemed equally important and its wide distribution throughout the tissues made it appear that resistance was a general rather than a local phenomenon.

Dead tissue excited no lymphocytic or plasma cell response, an observation which may be of considerable significance. Furthermore, the lymphocytic response about immunizing material was more distinct than that characterizing the ordinary foreign-body reaction of the rat. Most striking of all, perhaps, was the fact that the lymphocyte did not reappear when an immune animal was injected for a second time with tissues capable of inducing the refractory state.

Baeslack, who examined the blood of mice bearing inoculated tumors, found that regression was accompanied by an increase in the number of small lymphocytes....

Loeb (1915) and Loeb and Harter (1926) regarded the lymphocyte, in association with the connective tissues, as a defensive agent against both tumor grafts and those of normal tissues.... The lymphocyte reaction was thought to be, in part at least, a response of the host to tissue toxins rather than entirely a result of the development of immune substances, and its method of attack to be largely mechanical. Though it did take part in the destruction of an inoculum, it performed this office only under certain conditions; other factors, one of them the connective tissue, as already mentioned, undoubtedly shared in the process.

Mottram and Russ have also suggested the necessity for intervention by other agents, which, on account of the apparent lack of immune forces in the body fluids, they thought might be provided locally by the lymphocytes themselves. Like Da Fano, they could discover no accumulation of lymphocytes about dead tissue, nor could they find lymphocytes in the degenerated central portions of tumors. They therefore expressed the opinion that the lymphocyte was not a mere scavenger, but that it had an important role in the destruction of the Jensen rat sarcoma, the tumor with which their observations were conducted.

"Russ, Scott, Chambers and Mottram were led to emphasize the need for an accessory factor by their observation that a rat with an extraordinarily high lymphocyte count might have nevertheless a growing Jensen sarcoma, whereas another, with a count but little above normal, might be immune. Other papers by the Middlesex group, in which these views are repeated or amplified, are those of Mottram, Russ, and Russ, Chambers and Scott.

"Sokoloff and Prat believed the lymphocyte and the macrophage to be important and protective forces in man, while Vaughan and Eppler attributed considerable weight to the large mononuclear leukocytes, which they thought determined whether or not a tumor would recur in human patients.

"Lumsden regarded the extravasated leukocyte, in conjunction with a factor existing in the blood, as an important defence against transplanted tumors.

"While many investigators have thus attempted to determine the significance of the lymphocyte in resistance to transplantable tumors, it is with the name of Murphy that the lymphocytic hypothesis is most intimately associated. Those who wish a full account of his work must be referred to his monograph, in which are collected the results of his own work and that undertaken in collaboration with Morton, Taylor, Nakahara, Hussey, Sturm, Maisin and Liu.

"Murphy started with the observation that the avian embryo had no protective mechanism against the growth of heteroplastic tissue until after the 18th day of incubation, when a method of defence was rapidly developed, to attain full force at the time of hatching. In an attempt to discover what tissue or organ was responsible

for this resistance, mammalian tumor grafts were transplanted into the embryo together with bits of normal adult chicken tissue. The effects of spleen were striking; the tumor was found to be largely necrotic, and encircled by small round cells. Marrow had a similar action though less complete, and either would inhibit growth of the graft even though placed at some distance from it after it had become established. All the other tissues examined proved to be inert.

"The adult brain had been shown to share with the embryo this lack of opposition to heteroplastic inoculation, and here again a fragment of spleen was found to embarrass the growth of the tumor.

"If the lymphoid tissues were as important factors in resistance as these experiments suggested, it should be possible to effect hetero-transplantation by lessening the activity of the lymphoid tissue, and it was found, in fact, that chicken and mouse tumours would grow in rats after the lymphatic system had been largely depleted by x-rays.

"But the lymphocyte proved to be equally essential in immunity to homologous tumors. Not only were its numbers increased in the bloodstream of immunized or naturally resistant mice after inoculation with cancer, but there was a corresponding enhancement of the rate of cell division in the lymphoid centres of spleen and lymph-nodes.

"Resistance to homologous tumours disappeared when the lymphocyte was eliminated by appropriate x-ray dosage, or the activity of the lymphoid organs suppressed by the injection of a large dose (0.7 cc.) of olive oil into the peritoneal cavity. On the other hand, stimulation of the lymphoid system by a small dose of x-rays, by exposure to dry heat (55°-65°C. for five minutes), or by small doses (0.2 cc.) of olive oil or certain unsaturated fatty acids, augmented the refractory state.

"Immunity to transplanted cancer having been found thus to manifest itself by a cellular reaction about the graft, it was desired to ascertain what relation this local response bore to generalized resistance. Two methods were found whereby a localized round cell infiltration could be elicited without at the same time inducing a general reaction; these were, the injection of foreign blood into an animal already

sensitized to it, and the production of an x-ray erythema. In both instances the local reaction conferred adequate protection against grafts inoculated into the area involved. The reverse condition--absence of cellular reaction in an animal with generalized immunity--resulted in a failure of the defensive mechanism. Thus the local reaction appeared to constitute the resisting force, and might be effective even in the absence of generalized immunity, whereas generalized immunity without local response did not prevent the growth of a graft.

"Repetition of the experiments with x-rays, heat and oleic acid on animals with spontaneous tumours confirmed the results with transplanted neoplasms, these three agents exerting a distinct effect upon the outcome of autotransplantation; and as the only detectable biological effect induced in common by the three was stimulation of the lymphoid apparatus, it appeared that this must be responsible for increased resistance to the growth of spontaneous cancer....

"Loeper and Turpin intensified the lymphocytic reaction about tumour implants by introducing fragments of various organs from other species. Mouse testis produced in the rat an especially active lymphocytic permeation, yet the growth of transplanted sarcomas by the side of which it had been introduced continued unchecked. Thus the lymphocyte seemed to express a reaction toward any ordinary irritant, rather than to possess the important and almost specific defensive power which had been attributed to it.

"Caspari suggested that the lymphocyte was an accompaniment and not a cause of cure....

"Increase in the circulating lymphocytes without stimulation of the lymphogenic tissue, particularly the transitory lymphocytosis following administration of certain drugs, was without effect on resistance to cancer, Murphy maintained, because the augmentation was caused by contraction of the spleen and a consequent expulsion of its lymphocytes, which, however, soon vanished again from the blood-stream.

"It does not seem to me that Murphy has succeeded entirely in establishing his position, in spite of the ingenuity with which his experiments have been planned and the patience with which they have been carried out. Yet, on the other hand, I do

not think that any of his critics have entirely dislodged him. After all, there is something to be said for the lymphocyte. The observation that dead tissues excite no lymphocytic response suggests caution in dismissing the lymphocyte as a mere scavenger. Again, if its function were merely to dispose of dead material it might be expected in large numbers about the necrotic centres of transplanted tumours, particularly as the presence of polymorphonuclear leukocytes shows that there is no barrier to the access of cells from the blood. Yet none was found by Mottram and Russ, as has already been said, and my own experience supports their statement; I have sought for lymphocytes in this situation, where polymorphonuclear leukocytes lay in large numbers, but have sought in vain.

"Perhaps the strongest hint that the lymphocyte may not be present simply as a scavenger is Da Fano's assertion that, although in previously untreated animals it gathered in profusion about any tissue capable of inducing resistance, it did not reappear, except perhaps in small numbers, when such an inoculation was repeated in an immune one.

"Yet in spite of all this, the lymphocyte fails when actually confronted by the tumor cell, and the proposal that some sort of connecting link is required between cancer and lymphocyte if protection is to be extended is at least worthy of consideration."

Peritoneum:

It appears to be resistant only because the tumor cell is unable to lodge on its slippery surface.

Reticulo-Endothelium:

Blockade of the reticulo-endothelial system appears to increase the susceptibility to cancer.

Spleen:

Partly because of its probable significance for bacterial immunity, but particularly on account of the superstition that it is free from metastatic attack, the spleen has received more attention than all other organs. Von Hanseman, however, found that it was frequently the site of secondary tumors. Many investigators succeeded in

implanting tumors into the spleen without difficulty.

Others mixed spleen with tumor before inoculation and all but one found that this caused inhibition of growth. A third approach was to study the growth of tumors in splenectomized animals. Unless the effect of splenectomy be so slight as to appear only upon microscopic examination as Mottram and Russ contended, it seemed safe to conclude that absence of spleen neither accelerates nor retards the growth of propagable mouse or rat tumors.

Testis and Ovary: Effects of castration were essentially negative.

Thyroid and Thymus: Experiments up to 1929 were inconclusive or contradictory.

Regression:

In order to endeavor to penetrate the mystery of immunity, the receding transplantable tumor has been carefully investigated. There was at first considerable doubt in respect to the relation between regression and resistance, for either one of two explanations seemed plausible: the neoplasm immunized the bearer, thus bringing about its own eventual destruction; or on the other hand, the tumor cells themselves suffered some change which prevented further proliferation and the host subsequently became refractory by absorption of products of their life or death as in the case of immunization with normal tissues.

Haaland (1909-1910) soon showed that the refractory state set in before even absorption began; hence, as Russell (1912) expressed it, the metabolic activities of the tumor cell rather than its death and autolysis were to be regarded as the means by which resistance was induced. Tyzzer (1916) also was convinced that an immune principle was elaborated long before the tumor was destroyed.

Additional evidence that the host was responsible for spontaneous cure was offered by Mottram and Russ, in the fact that the same tumor emulsion gave rise to both growing and receding tumors, and Woglom's experience fully corroborated this.

The host's attack probably begins at the margin of the growth. The prolonged conflict which ensues shows how closely balanced are the tenacity of the tumor cell and the curative forces of the organism, and explains the four types of neoplasm described by Mottram and Russ, and so thoroughly familiar to all who have had any

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experience with transplantable new growths: (1), the "progressive" tumor, which steadily increases in size; (2) the "retarded" tumor, in which the growth rate gradually diminishes as the tumor increases in size; (3) the "oscillating" tumor, which after reaching a certain size, oscillates between narrow limits for long periods of time; (4) the "disappearing" tumor. To these may be added a fifth type, that which recedes until it seems about to disappear and then increases steadily in size again.

Hypersusceptibility:

According to Chambers and Russ immunity seemed to follow when tumor cells died under conditions which insured intimate contact with an active circulation; hypersusceptibility, on the other hand, when they were allowed to autolyze before inoculation or were subjected to conditions favoring rapid autolysis, such as mechanical disintegration, washing with so-called physiological fluids, or increased temperatures (Woglom, 1929).

Comment: Thus in the treatment of human cancer it appears that the vascularity and permeability of the tissues in the tumor bed are of great importance. It also would seem best not to destroy a tumor too fast by too aggressive toxin therapy or radiation, in order to produce the most effective immunity.

Tumor Immunity

Clemmensen (1938) discussed various methods which had been used up to that time in attempting to produce tumor immunity.

"The power to induce resistance is possessed not only by tumor tissue but by practically all kinds of homologous tissue, except a few such as the lens of the eye, brain, or kidney (Itami, 1926). The majority of investigators have held, however, that the tissue must be living. More recent investigators seem to indicate that this condition is not an absolute one. Thus Woglom (1933) succeeded in inhibiting the growth of rat tumor by mixing it, prior to inoculation, with tumor cells which had sojourned for some days in the subcutaneous tissue of an immune rat. These cells had been killed by freezing and thawing; but Woglom will not deny the possibility that the protoplasm may still have been living.

Clemmsen noted that spleen, which is exceptionally effective in producing immunity, is very likely to cause infection, and the same is true for liver, which is less effective. The most serviceable is fetal skin (Tsurumi, 1915), as it is easy to obtain in a sterile condition and readily produces a high degree of resistance. Itami (1926) believes that the skin of grown animals is just as powerful an inductor.

Clemmsen noted that the lymphocytes and leukocytes possess protective power, as reported by Bashford, Murray and Haaland (1908). Washed erythrocytes will not induce resistance (Itami, 1908).

According to Bashford, Murray and Haaland (1908), the increase in resistance is greater the more nearly the inducing tissue and the indicator approach each other genetically. This agrees well with another observation they made: that the protection is stronger against the tumor used to produce the immunity - against which it is often absolute - than against any other tumor. The resistance-inducing quality is to a certain extent specific, and the consequence of this must be that to obtain the highest degree of immunity possible, the same tumor should be used. (Comment: It is of interest to note that patients who have recovered from one type of neoplasm following toxin therapy, an acute concurrent infection or an acute inflammatory or febrile episode, may develop some other type of cancer many years later. At least 46 such cases have been found, of which 26 proved fatal.)

Clemmsen stated that good producers of immunity are often very rich in cells, but no single factor has been found to be the determining one for the power to induce resistance. The following seem to play a part: 1. the quantity used to induce immunity (successes more numerous when dose is reduced, though the reverse effect has also been noted); 2. In reimplantation the dosage is also important. A large graft may break down an increased resistance, which might have been proof against a lesser dose; but here the susceptibility of the inoculated tumor to the induced resistance is an important factor as well, since it varies considerably from one tumor strain to another. Woglom (1929) showed that certain transplantable tumors are able to defy the refractory state, and tumors are occasionally found against which no resistance seems to have any effect. If the vitality of the tumor has become reduced through exposure to heat

or radiation, its susceptibility to an immunity caused by living tissue is increased.

That the cause of a tumor's regression must probably be within the host was shown by Woglom (1925), who found that Jensen's rat sarcoma even while regressing was able to produce growth on transplantation to normal animals. He found besides that the animals with regressing tumors were refractory against fresh inoculation, while such inoculation might give both positive and negative results in animals with growing tumors. From this he concluded that some animals are more readily immunized than others. (Comment: In studying over a thousand cases treated by toxin therapy, one ^{also} finds that certain patients are more easily immunized than others.)

As to the time when immunity begins, the consensus of opinion of the earlier investigators seems to be four days after inoculation of the inductor, reaching a maximum 12 days later, and lasting three weeks. (Woglom mentions a period of as much as six months.)

Clemmsen concluded: "It is natural to subscribe to the view held by Murphy (1913) and subsequently upheld by W.E. Bullock (1915), Tyzzer (1916) and Bittner (1931) that it would seem much more likely that there is a defensive mechanism whose strength and rapidity of action depends upon the degree of relationship, being more prompt and violent the more foreign the tissue introduced."

Tumor Transplantation and Exposure to X-ray:

Clemmsen reviewed the literature and stated: "It thus seems justified to conclude that the general exposure to x-ray prior to inoculation lowers the resistance to implanted homologous leukoses and tumors. If the resistance is particularly strong, such irradiation is not sufficient to produce a positive result by general exposure to x-ray. On the other hand, evidence has been adduced that makes it likely that a resistance induced in normal tissues may under certain circumstances be overcome by this same means, and that a resistance induced by tumor tissue may be temporarily overcome by exposure to x-ray."

Demonstration of a Lowered Resistance against Heterotransplants as a Result of Exposure to X-ray:

Clemmsen himself demonstrated that "Operative implantation of 6 - 8 ctgr. of

Crocker mouse sarcoma 180 from mice of a Bagg strain into 114 white and black and white rats previously irradiated with 460 - 575 r resulted in the development of tumors weighing as much as 15 grams and over. All the x-rayed rats that were alive on the 14th day after inoculation had nodules larger than the original graft. In the 96 normal rats in the control, no similar phenomena were observed. The tumors eventually recede, but the mortality of the rats is considerable as a result of radiation, especially in the second week.

Serial Passage of Mouse Sarcoma 180 in X-rayed Rats:

Clemmsen found that he could keep tumor cells alive in x-rayed rats first for 85 days and later for 55 days as proved by biological criteria (their subsequent successful reinoculation into mice.)

It has thus for the first time been found possible to keep tumor cells alive in an x-rayed foreign host for a period longer than that which they are capable of surviving in a normal animal of foreign species. (Comment: These findings suggest that in treating patients with toxin therapy who have had preliminary radiation one should give more prolonged toxin therapy in order to destroy all viable cells, and overcome the immunosuppressive effects of radiation.)

The Relation between Heterologous Tumor Immunity and Exposure to X-ray:

Clemmsen then performed an experiment which showed that the growth of heterologous tumors in x-rayed rats could be prevented by provoking tumor immunity: i.e. rats which had been previously immunized by inoculations of mouse sarcoma 180, 44 to 157 days prior to irradiation and reinoculation. It was found that in both normal and x-rayed rats inoculation of mouse sarcoma 180 develops considerable resistance, that is, "the growth of heterologous tumors in x-rayed rats can be prevented by provoking tumor immunity." Clemmsen surmised that the x-ray effect merely delays the process whereby an organism defends itself against cancer.

The Respective Effect of X-Radiation Before and After Transplantation:

Clemmsen concluded that his experiments indicated that x-rays have the effect of inhibiting the self-immunization temporarily, provided the exposure takes place very shortly before transplantation, but that if immunity has become fully developed (44

to 153 days after inoculation), the exposure to x-ray has no effect on immunity.

(Comment: These findings are significant as they relate to the use of radiation in cancer patients who are to receive toxin therapy. Many case histories have been found which clearly indicate that when toxins are given first and thus are able to strengthen whatever natural immunity already exists by causing necrosis and absorption of tumor tissue, subsequent radiation is apparently enhanced (complete regression of radio-resistant tumors). However, if heavy radiation is given first, and the immunity of the patient is thus suppressed subsequent toxin therapy does not appear to be nearly as effective as in patients who have had no radiation.)

Histological Investigations into the Interrelation Between Heterologous Tumor

Immunity and Exposure to X-ray:

The early investigations on immunity to heterologous tumors are few and contradictory in results. They are, however, closely connected with the so-called "lymphocyte theory."

Clemmensen then reviewed the work of DaFano (1912) who found that with inoculation of homologous tissue, lymphocytes will gather in great numbers around any such graft capable of provoking tumor immunity, while dead tissue, which has no corresponding immunizing effect, does not call forth a similar cellular reaction. When an inoculation is repeated in an animal already immunized the said reaction does not appear. From this experiment DaFano concluded that the intimate connection of the lymphocytes with the immune process must be practically certain.

His observation gave rise to a rather extensive literature. (See Woglom, 1929, and Murphy, 1926 for references). Murphy and his group elaborated the theory of the important part played by the lymphocytes in the matter of tumor immunity. Thus, they maintained that under certain conditions where the organism is poor in lymphocytes, either locally or generally, a decreased resistance is observed both to homologous and heterologous tumors. On the other hand, an increase of cell division in the lymphoid centers (spleen, nodes) indicating a stimulation of the lymphatic system, was observed after inoculation of tumors into immunized or naturally resistant mice; and the resistance could be increased still further by stimulation with small doses of

x-ray, or by injection of small doses of olive oil. Moreover, Murphy claimed it was possible to increase the resistance to spontaneous tumors.

It was further pointed out, in support of the lymphocyte theory, that tumors with an abundant peripheral zone of lymphocytes often grow slowly, and metastasize late, and that a corresponding relation between the fate of the graft and the degree of lymphatic reaction is found in transplanted tumors.

Clemmensen stressed that "heterologous tumor immunity is the result of self immunization provoked by the transplant."

Both heterologous and homologous tumor immunity can be reduced one step by pre-exposure of the organism to x-ray. However, when manifest (complete) heterologous immunity has become mobilized, it cannot be influenced by radiation, i.e., it is so strong that it cannot be broken down, or it is not susceptible to x-ray action. Or heterologous resistance may contain two elements, an x-ray susceptible, which accounts for resistance during the first two weeks after the primary inoculation and an x-ray resistant, which provides the necessary defense after that time and under subsequent inoculations.

Clemmensen then reported on his experiments on mouse sarcoma 180, in normal rats, immunized rats, x-rayed rats (520 r) and normal rats. Group N: Normal Rats: 24 hours after transplantation there is marked degeneration of the nuclei of the graft, and numerous polymorphonuclear leukocytes invade it. At the periphery, tumor cells of normal appearance are mixed with lymphocytes and monocytes, from which they are easily distinguished by their large nuclei. The whole graft is surrounded by an exudate composed of lymphocytes and monocytes as well as polymorphonuclear leukocytes, among which are many eosinophils. Some proliferation of the tumor cells is seen during 4 to 6 days, but soon these cells are surrounded by lymphocytes and monocytes, and after six days the graft becomes necrotic and encapsulated.

Group I, Immunized Rats: First day: In contrast to the above, all tumor cells are degenerate. The graft is invaded by polymorphonuclear leukocytes, a similar peripheral exudate is present. From the fourth day, infiltration of mononuclears is seen, and the graft is enclosed in a capsule, which during the second week shows no alterations.

Group X, X-rayed Rats: "From the beginning, this group is distinguished by a comparatively great number of tumor cells of normal appearance. During the growth and subsequent retrogression of sarcoma 180 in x-rayed rats, mononuclear reaction is very slight or entirely absent, and cannot be considered to play any significant part."

Group I plus X, Immunized and Subsequently X-rayed Rats: First and second day: tumor cells degenerated, and the center of the graft is invaded by polymorphonuclear leukocytes, the same as in immunized rats. In the surrounding exudate are a few cells, mostly polymorphonuclear leukocytes. The chief characteristics of this group are the rapid death of the sarcoma cells and the absence of mononuclear reaction.

Clemmsen concluded that the immunity to heterotransplants does not depend solely on the round cell reaction in any of the ways that DaFano and Murphy based their theory. Clemmsen concluded that other factors operate together with the mononuclear reaction: thus, that part of the organism's defense which is susceptible to x-ray is connected with the cellular reaction and exerts its energy during the first two weeks after the transplantation; while after that time a defense is set up which is independent of the cellular reaction and insusceptible to x-ray. (Clemmsen, 1938. He gives several pages of bibliography.) Comment: These experiments suggest that in treating cancer patients, we should attempt to stimulate the resistance first, by toxin therapy, and then it may be advisable to use small doses of x-ray therapy, thus utilizing the destructive action of radiation without the danger of reducing the patient's existing immunity or hastening the development of metastases. Clemmsen's work seems to suggest the disadvantages of preliminary radiation, prior to surgery or toxins. There are several cases on record of patients in whom preliminary acute infection occurred, or toxin therapy was given, and later x-ray was administered. These patients showed a surprising response to the radiation, and recovered completely even when the tumor was a radio-resistant type, and the prognosis had appeared entirely hopeless.

Touraine and Duperrat (1938), in a paper on the spontaneous cure of cancer, stated that the French medical public was not sufficiently familiar with this phenomenon. They believed that Lomer (1903) was the first to publish an important work on 203 cases of regression of cancer. A considerable number of these were inoperable cancers of the uterus which were cauterized. Some of them lacked microscopic confirmation of the diagnosis.

Further cases were assembled by Mohr (1903), Gaylord and Clowes (1906), Handley (1909), and especially Theilhaber and Edelberg (1913).

In 1918 Rohdenberg reviewed the question and analyzed 302 cases of cure or spontaneous regression of which 192 appeared unequivocal. To that study, which has since been regarded as a classic, have been added others of less importance. Beck and de Courcy readily admit that this phenomenon does occur, and stress its great interest.

Beck (1933) reported in the *Traité de Jadassohn*: "One can affirm that there are spontaneous cures of skin cancers. Both clinically and histologically, one has proofs of the arrest of their vitality proceeding to spontaneous cure.

French oncologists accept this cure, but consider it as being very rare. Ménétrier made a critical study of the published cases and regarded only 148 of Rohdenburg's as definitive. He regarded their number as being of importance. "Moreover, their interpretation is supported by histological and experimental studies. Cases of spontaneous regression are common in the history of experimental cancer of mice."

As to its rarity, Bashford believed it occurred once in 100,000 cases. In any event, it is possible that it is less exceptional. Certain cancers may remain unrecognized and may have regressed spontaneously before they were apparent. This hypothesis rests on certain observations of cases in which no primary tumor could be found, but lymphnode metastases developed. (Butlin, Williams, Sézary, etc.) In such cases the primary tumors must have been absorbed.

1. Clinical Types of Regression:

Complete cure implies the disappearance, more or less rapid, of all the neoplastic tissue. In addition to the cases assembled by Frauchiger (1929), Rohdenburg (1918) assembled 20 cases of skin cancers. Godfrey (1910) published a case of inoperable cancer

of the base of the tongue, the tonsil, and the pharynx, verified histologically.

The patient was sent home to die and the only treatment was to wash his mouth. The tumor entirely disappeared, leaving supple scar tissue; traced 18 months.

Other even more striking cases have been published of cancer of the skin with biopsy, not only of the neoplasm, but of the scar tissue after regression took place (Ferguson Smith, Neageli) (1897).

There is partial cure when the cancer disappears in one area at the same time that it develops in another. A good example of this was given by Ducuing in his *Précis de Cancérologie*: an infiltrating basal cell epithelioma of the lower lip, which healed itself along the lower edge while progressing on the upper side. It appeared to be completely healed several times, finally a "colloidal shock," produced by a subcutaneous injection of milk, cured it again.

In a patient of Nicholas, Massia and Weigert, a spindle cell epithelioma of the back of the hand healed in its central area and was replaced by scar tissue. The same thing occurred in a case of spindle cell epithelioma of the loins observed by Dorffel.

Shaw Dunn and F. Smith (1934) also verified the process of cicatrization histologically in an analagous personal case.

Sometimes the primary tumor disappears completely, although the metastases proliferate. Walsh published a case of breast cancer of two years' duration in which the patient died of cerebral metastases. At autopsy he found that the primary tumor had completely disappeared. Peterson and Colmers resected a cancer of the pylorus but had to leave many cancerous nodules. The patient died 18 months later of intestinal obstruction due to an umbilical hernia. At autopsy the cancer nodules had disappeared, although there were some hepatic metastases.

The opposite has also occurred: while metastases are absorbed, the primary tumor continues to increase in size. Theilhaber and Edelberg (1913) noted how often tumor cells penetrate by breaking into the veins and the lymphatics and are seen in the circulating blood (Goldmann, Schmid, Borrel, etc.), and yet how few of these emboli produce metastases which actually grow. Schmid has studied the process of regression of these cancerous emboli in the lungs, a process he has observed in 15 out of 41 cases of

various types of cancer. Handley has seen four cases of spontaneous fracture of bony metastases. Though all these patients ultimately died of their cancers, the fractures had consolidated and the bone metastases had disappeared. Theilhaber and Schuchardt have reported that at a second laparotomy, they found complete disappearance of cancerous nodules in the peritoneum ^{that had} developed in the course of ovarian or gastric carcinoma.

In other cases there is a temporary regression: the tumor disappears without apparent reason, only to recur. Osler's case, one year after mastectomy for breast cancer, had paraplegia and metastases in the sternum, right eye, and in the pleura. Two years later all these had disappeared, and she even regained her eyesight ^{and} returned to her former occupation. The cure was only temporary, and she later died of cancer.

It is not absolutely exceptional to observe in a cachectic cancer patient complete, rapid disappearance, in a few days, of all or almost all the tumors. Their reappearance a few days later slightly precedes death. This curious "eclipse" was reported by Rohdenberg. A generalized lymphosarcoma, of six months' duration, disappeared the night of February 6, 1917. A week later the lymph nodes regained their original size, and death occurred on March 5, 1917. Schkarin, and Mackay (1907) published similar cases.

One must also consider the extraordinarily slow progress of certain cases. Handley observed a case of breast cancer which in 28 years had had periods of prolonged arrest, during which metastases disappeared.

Discussion: In all the preceding cases the regression of the neoplasms is unequivocal; they were reported by observers of recognized experience and honesty, either clinically, or anatomically in the course of a second operation or autopsy.

One must remember, in evaluating the size of malignant tumors, the importance, sometimes marked, of the pericancerous inflammatory reaction. Cleanliness, palliative intervention, internal medication (anti-syphilitic treatment, opotherapy, lecithin, antiseptics, etc.), often suffice to cause the enormous swelling to disappear. One should only consider as unequivocal cases in which there is microscopic proof of malignancy.

Many investigators question the histological findings or else they consider that if a tumor regresses spontaneously it cannot really be malignant. This latter objection Touraine and Duperrat felt to be unwarranted.

2. Conditions of Spontaneous Regression. All cases were excluded in which the cancer had been directly attacked by surgery, radium or injections of radioactive salts.

a. Local circumstances: In a first group of cases, there was no local intervention whatever, not even biopsy. (Godfrey's case cited above) This was true of certain skin cancers in which the clinical findings were sufficient to confirm the diagnosis of epithelioma: Wise, Tauber, Goldman, Balban.

Incomplete Surgical Removal: Sometimes a simple biopsy to confirm the diagnosis. Rohdenburg's case presented a non-ulcerated spindle-cell epithelioma of the external palpebral angle. A biopsy caused a violent hemorrhage which required a ligature. The tumor rapidly flattened around the seventh day. A pneumonia caused death five weeks later. Serial sections confirmed the disappearance of the epithelioma, found at biopsy.

Cusani's patient had a deep ulcerated spindle cell epithelioma of the dorsal surface of the foot. The only treatment consisted of sterile dressings. Clinical cure was complete in six months, and was verified by two or more biopsies. Shaw Dunn and F. Smith's case was similar, the site being Scarpa's triangle.

Sometimes incomplete removal was done because the tumor was too extensive or too adherent to the adjacent tissues. This was true in many cancers of the pylorus or the uterus, assembled by Rohdenburg, Theilhaber and Edelberg. Schuchardt's case is cited, where a partial resection of an advanced gastric cancer was done, leaving the disseminated peritoneal metastases and chyliform ascites. Two years later the patient died of pleurisy. Post mortem revealed no ascites and no peritoneal metastases.

In certain cases of cancer of the pylorus or intestine an "opération de dérivation" was practiced. Czerny published 11 such cases in which the patients survived from 2 to 14 years. Chevrier and Dalsace reported a case of a female, age 52 years, who had a gastroenterostomy in January 1930, for a juxta pyloric tumor of the posterior wall of the stomach, 4 cm. in diameter. On June 14, 1930, a second laparotomy was performed and revealed that the tumor had disappeared. Palpation revealed

a little glandular nodule which did not infiltrate beyond the muscularis mucosa.

Sometimes the intervention is limited to a surgical laparotomy (Williams, Boldt (1908), Rohdenburg (1918), etc.) In Clarke's case, an inoperable cancer of the stomach with metastases to the mesenteric lymph nodes, the patient remained in perfect health nine years later.

Finally, an inoperable cancer was often treated only partially by cauterization, with or without curettage. Regression or cure was noted in such cases by Chrobak (1905), Lomer (1903), Liek (1928), Prochownik, Weindler (1907), Frankel (1901, 1905), Schröder, and many other cited by Theilhaber. The authors cited one such case of Delbanco's in which a cancer of the breast was incompletely removed by electrocautery.

In a third group of cases, regression of cancer followed local infection. We have long known of cases of tumors which have completely disappeared following erysipelas: epithelioma of the skin, Coley (1893), de Gaetano (1903), Jersild, Réding (1928), etc.; breast cancer, Czerny (1907), Papadopoulou, etc.; testicle and sarcoma, Bolognino (1907-08); lymphosarcoma, Watson (1902), etc. In all the cases erysipelas was accompanied by high and prolonged fever. The cures thus obtained may be considered as definitive since some of the patients were followed 20 years.

The voluntary inoculation of streptococcus was done by Kleeblatt (1890), in an inoperable lymphosarcoma of the ear and by Coley (1891, 1893) in a sarcoma of the neck. In these two cases the results were favorable and Coley's patient remained without recurrence eight years later.

b. General Circumstances: These have been carefully analyzed by Thielhaber and Edelberg (1913) and by Rohdenburg (1918). These authors and also Lomer have assembled certain cases where the regression of a cancer appeared to be associated with a high fever lasting several days. Whether this temperature was due to small pox, Riffel (1901); pneumonia, Kutzner (1889); malaria, Loeffler (1901), Avromovici (1907); acute tuberculosis, Sigg (1891); or suppuration at a distance, Perrin (1891). The condition needed seemed to be the fever during several days.

Such conditions are difficult to achieve artificially even if lysates, vaccines or hot air are used - the authors had not discovered any one who had used diathermy.

"Rohdenburg noted that one of these cases, a female age 37, (in which laparotomy had revealed an enormous mass on the lateral wall of the pelvis, and microscopic examination showed it to be a fibrosarcoma) developed a very painful sciatica following operation, for which she was given "hot air baths." To the surprise of all, the patient recovered completely. She died 20 years later of uremia, and a careful autopsy revealed not a single cancer nodule."

These reports nevertheless, do not permit more general conclusions. The opposite may occur: one has seen certain cancers progress more rapidly under the influence of fevers. Brisset has observed on two occasions, that a lymphangitis of the hand and arm had precipitated a recurrence of cancers of the breast. In another case, it played a part in a large recurrence on the surface after a grippy pleuropneumonia. In one case of Nicolas, et al., a breast cancer which had been heavily irradiated, the general health remained excellent until a lobar pneumonia developed with fever, which was followed by "lymphangitic cancerization of the skin."

In two especially curious cases, one had the impression that the regression of the tumors (temporarily) was associated with absorption of exudates. The first such case, a scirrhus of the breast, MacKay operated in 1904, and it soon recurred. In 1906 the patient was cachectic and presented a pleurisy and a voluminous metastatic mass in the opposite axilla. In a few days the pleural exudate was entirely absorbed, the cough, the dysphagia and the axillary metastases all disappeared. This amelioration was only temporary, as the patient died three weeks later. (MacKay, 1907)

The second better known case (Hodenpyl, 1910) had multiple recurrences of breast cancer with metastases to the liver and chyliiform ascites; nevertheless, four years later there remained only the ascites. This fluid was injected into cancer-bearing mice and cured them. Hodenpyl then had the idea of treating 47 cancer patients with these same injections. He observed the tumors diminish in volume and noted that the injections were followed by local reactions at the site of the neoplastic masses, redness, sensitivity, and tumefaction.

These cases have raised the problem of the therapeutic action of cytolsins. Furthermore, one must note the existence of serous effusions, often mentioned in

the observations on spontaneous regressions of cancers.

The role of pregnancy on tumors is disputed. It seems that in the great majority of cases it aggravates the disease, and reciprocally, its termination may be favorable. Jahr (1894) observed a sarcoma of the axilla, with numerous metastases, rapidly progress in a pregnant woman. Following therapeutic abortion, all the tumors disappeared.

In other observations, artificial menopause helped cause regression of the tumors (Pearce Gould).

Certain reports indicate that severe hemorrhages may exert a very favorable influence, and may even be followed by "unexpected cures". (Lomer, Kaltenbach and Leopold, Theilhaber)

Finally, in other cases, the resorption of malignant tumors occurred after diverse internal medication, without any local treatment of the tumor.

When epithelioma develops in a syphilitic lesion or in an old syphilitic case, specific treatment may cause amelioration and even rapid cures. A patient of Touraine and Solente presented syphilitic ulcers on the palm of the hand, which several histologic examinations proved to be spindle cell epithelioma. An energetic mixed treatment with arsenic and mercury was followed by an amelioration from the fifth day, a cure which was maintained three years later. Limouzi's patient had a vast ulceration of the nose and upper lip of six months' duration. The serological reactions were strongly positive for syphilis, but biopsy revealed spindle cell epithelioma (confirmed by several pathologists). Mixed treatment with arsenic and bismuth produced a complete cure which was maintained two years later. The observations of Kolopp, Levy, Franckel, and Touraine are almost identical: cancers of the face, verified histologically, were completely cured by specific treatment. Injections of bismuth alone caused the regression of the vegetations of a spindle cell epithelioma reported by Pinard.

It is evident that, interesting though they are, these cases do not permit a generalization. One would be in grave error to attack all cancers by antisyphilitic treatment.

One has, nevertheless, often noted that a series of injections of cyanide of mercury produces a diminution of the neoplastic masses and a decrease in their adherence to the surrounding tissues. But this diminution is only temporary, and can only be used to facilitate surgical removal.

Other internal medications against cancer have frequently been extolled. Juster, Cailliau and Huerre are said to have obtained cures in diverse cancers of the face with injections of lecithin into the tumor or at a distance. Werner (1912) is said to have done so with choline, Clay with turpentine, Liebreich with cantharides, Behla with lysol, Zeller with silicic acid, Burov with calcium chloride, Delbet with magnesium salts, others with colloidal metals (copper, selenium, etc.) Yeast extracts have given important ameliorations.

The results from these diverse therapeutic methods are, nevertheless, irregular. One would not be able to generalize.

3. Histologic Types of Cancers that are Spontaneously Curable: Rohdenburg's study (1918) on 102 cases lists 159 epithelioma (squamous cell, pavement cell or parenchymatous); 2 endothelioma, 24 sarcoma, 7 chorioepithelioma. Of 14 cases of skin epithelioma, histologically proven, and spontaneously curable, which Touraine and Duperrat had assembled, 11 were squamous cell and 3 basal cell.

Among the epitheliomas, some have a very special appearance, and all surgeons have seen papillary ovarian carcinomas with numerous peritoneal metastases, regress markedly after laparotomy, to the point of sometimes giving the impression of cure. Flesch published an excellent case in 1927.

All types of sarcomas have been observed, and also malignant melanoma has presented an atypical evolution which was benign or slow. (Handley (1906, 1907), Matthews (1915)).

Finally, the spontaneous regression of choriocarcinoma does not seem to be exceptionally rare. In a recent case of Renzi and Erez in a female age 25, hemorrhage was so persistent that laparotomy was necessary to ligate the hypogastric arteries, but this proved impossible because of the presence of choriocarcinoma verified microscopically. A year later the patient's cure remained complete, and was

verified histologically. Noble (1902), Marchand (1895), Hormann (1904), von Franque (1903) all observed unhoped-for regressions in this type of tumor and even of its metastases.

4. Histological Process of Spontaneous Cure: The comparative studies of tumors healed by radiation and especially cancers of animals (quite often spontaneously curable) permit one to understand the histologic process of spontaneous regressions of certain cancers.

Even though the phenomena observed in man and in animals is not exactly identical, the detailed study of Roussy and Leroux (1922) on experimental tar cancers has a great value for clarifying the mechanism of cure in man.

The cancers in the process of regression are surrounded at the start by a granulation tissue which is formed by "leukocytic infiltrates", especially composed of lymphocytes, but also of plasma cells, giant cells and macrophages or vacuolar cells of Renaud and Lacroix.

It is not rare to encounter, in addition, capillary lesions of which the endothelium may even be thrombosed. It is to this that Woglom accords the principle role in spontaneous regression.

Later this granulation tissue is progressively invaded by a sclerotic reaction which usually starts at the center of a neoplastic mass, more rarely at the periphery. (Jacobsthal (1907); Shaw Dunn (1934)). It produces a strong surcharge of stroma by thick bands of collagenous tissue, sometimes associated with hyperplasia of the elastic fibers, more often accompanied by abundant vascular new growths and by thrombosis of the lymphatics (Renaud and Barjon). The sclerotic tissue dissociates the epitheliomatous masses, fragmenting them into islands. On contact the cancer cells sometimes undergo an early horny maturation, while the central cells remain undifferentiated. There results an aspect inverse to that of horny pearls, with axial keratinization. This peripheral keratinization represents the principal manifestation of the process of cure for Shaw Dunn and F. Smith (1934). In other cases, certain cancer cells show hyaline degeneration, ^{as described by} (Proescher ^{and} or Follmann) or a necrosis followed by calcification Wells (1908), Beck (1933), Rohdenburg (1918).

But the order in which these diverse processes occur is not always easy to establish. Does sclerosis occur because a cancer is "sick" or does the cancer regress because the sclerosis progresses? There is a debated question to which it would seem that we may give a second answer.

5. Preliminary Remarks on Pathogenesis: To what may we attribute this complete reversal in the evolution of tumors which usually continue to grow? Certain cancers have regressed under the influence of local circumstances, i.e., simple biopsy or partial resection. In these cases, the death of the cancer cells may be due to ischemia. Rohdenburg (1918) gives an example of an epithelioma of the face which he cured.

In cases where severe local infection occurred the process had the effect of causing purulent necrosis of all the tumor and thus effected a veritable exeresis. If the infection is more benign, it produces infiltration of the cancer tissue by lymphocytes. Ribbert (1911), Bayer (1910), Da Fano (1910, 1912), Murphy (1926), Rubens-Duval (1914), etc., believe that lymphocytes have a destructive action on cancer cells, and this action appears to be confirmed by certain experimental studies.

When the regression of a tumor occurs under the influence of "general circumstances," i.e., systemic effects, its explanation is even more difficult.

One has asked if simple general anesthesia may provoke a disequilibrium of lipid metabolism or of the sympathetic nervous system. Gaylord and Simpson do not admit that this can be the case, for they have observed experimentally that the disease progressed after inhalation anesthesia.

The role of fever appears less negligible. One has observed that when a laparotomy was followed by amelioration of the cancer, it was precisely when it was accompanied by a temperature which remained high for some time.

Perhaps fever acts, as some think in the United States, in provoking local thrombosis favored by the hyperinosemia and the hyperviscosity of the blood in fevers. Perhaps also the modifications in the acid-base equilibrium should be taken into account. Cancer patients are often alkalotic. Réding has noted a slight temporary acidosis in a case of cancer of the cheek cured after erysipelas. In the same way does a normal or slightly augmented calcium content, succeeding to the habitual hypo-

calcemia of cancer patients, constitute a favorable element?

One knows also that the metabolism of hydrates of carbon, and especially of sterols, is disturbed in cancer. The sterols comprise in addition to sterol and vitamin D the majority of the sex hormones. The action of these hormones on cancer has been the subject of studies that are frequently contradictory. Sannic and Alphandéry devoted a recent general review to the subject. Sézary noted that injections of a testicular extract very often are followed by marked relief of pain, a cleansing and diminution of cancers of the skin, the tongue and of lymph node metastases of adenosarcomas. In other patients folliculin (estrone) appeared to give the best results: one also recognizes the action "frénatrice" of castration, the stimulating action of the extracts of genital glands, the inhibitory role of insulin on the growth of sarcoma. By injections of estrogen, Lacassagne produced adenocarcinoma of the breast in male mice.

The authors then called attention to the hypothesis of catalysins, of cytolysins raised by Hodenpyl (1910) and De Courcy (1933) and not verified. The theory of inflammation attributes the fact that young people are less often subject to cancer to the fact that their organism is capable of intense inflammatory reactions. Lohmann (1931) has actually demonstrated that cells of epithelioma can survive a certain length of time in the body fluids of the organism and in the physiological serum, but that they die very quickly when placed in the exudate produced by vesication.

Finally, Dustin devoted himself to the difficult study of the action of the products of necrotic cancer cells on the remaining neoplastic cells. He admits that these necrotic products may play a catalytic role dangerous at first, later useful. Rubens Duval (1930) thinks that in this way slowly but progressively, immunity to cancer is acquired.

The spontaneous cure of cancer is thus possible, even in a very advanced stage. Certainly, this eventuality seems to be very exceptional and could not in any way modify the prognosis and the treatment of the disease.

Nevertheless, the question is important theoretically, because it implies that the evolution of cancer is not always or absolutely fatal.

It has also a great practical interest, for it proves that, in certain local or systemic circumstances, regression and even cure of certain malignant tumors have been obtained. Thus are indicated various avenues in which future studies may be directed. (Touraine and Duperrat, 1938 - they gave 25 references)

As regards spontaneous regression of various tumors, Ewing (1940) states that "spontaneous absorption of implanted tumors was first recorded by Loeb, and its comparative frequency and the increased resistance to re-inoculation were emphasized especially by Clowes and Baeslack (1905-1906). . .The histologic changes in regressing tumors vary widely. . .Phagocytic processes by mononuclear cells are frequently observed (Gaylord, Clowes and Bashford). In angioma they may occur "as a result of contraction of the capsule, thrombosis, inflammation or ulceration, or a cure may be affected by continuous pressure, ligature of the vessels or excision. Very slight interference may be sufficient. Intercurrent diseases or cachexia may initiate the regression." (p. 256) In giant cell tumor of bone he stated that "spontaneous cure is sometimes observed, but the natural termination is death from hemorrhage and infection, after the growth has reached large dimensions (and caused much destruction of bone". (p. 318) ... "There is little tendency to spontaneous regression in the average case, and yet not a few records exist of a spontaneous cure, some after fracture". (p. 147)

Ewing stated that a remarkable feature of juvenile nasopharyngeal fibroma attested by many observers was its tendency to complete spontaneous regression after partial removal (Bensch, Grunwald, Konig, Bruns, Zarniko). "This seems to occur chiefly toward the end of the period when the tumor may develop, i.e. the 25th year. There is thus illustrated a form of natural immunity... ." (p. 180-181)

In Kaposi's sarcoma he noted that spontaneous cures have been reported. (p. 281)

As regards lymphosarcoma he noted that "Not a few cases have been reported as cured... Ruff (1906) has collected a series of more recent reports illustrating the regression of lymphosarcoma after infectious diseases and irradiation. Koschier (1910) reports regression of a tonsillar growth after removal of a portion of tissue for diagnosis, followed by a recurrence in the abdomen. Longcope reports the complete spontaneous disappearance of extensive lymphosarcomatous tumors followed by death from asthenia." (p. 423)

Spontaneous changes and regression may occur in congenital tumors such as neuroblastoma and other tumors of the sympathetic system.

As regards cystic ovarian tumors, Ewing states that "as a rule they are of moderate malignancy and slow growth. Calcification is a striking feature of the epithelial elements in certain tumors, mainly those of the serous type and marked papillary structure. It indicates a limited degree of growth capacity and a tendency to spontaneous regression. (p.648)...Spontaneous regression is a remarkable feature observed in a well-attested group of cases. These are usually of the papillary type and low grade malignancy; often exhibiting calcification in the primary growth. The process has been described in detail by Troschel, Bumm, Freund, Fraenkel, Pfannenstiel and others. The regressing nodule is found enclosed in fibrin, granulation tissue and multiplying endothelium, which cuts off nutrition, leaving a flat scar. A very long observation is required before regression may be assumed, since recurrences have been noted after from 15 to 21 years (Malcolm, Opitz, Pozzi), and in the line of incision after 21 years (Olshausen).

"Spontaneous cure is observed with certain tumors under peculiar conditions.... Inflammation about the borders of, or in the body of the tumor, seems to cause occasional extrusion of certain sarcoid growths of the skin (Randolph Watson). Accidental infection by erysipelas has been followed by spontaneous regression of sarcomas.... A local or general immunity seems to be the only explanation of an increasing list of spontaneous cures of highly malignant tumors.

"Most of these cures are only partial. Among them are sarcomas, squamous epitheliomas, and adenocarcinomas."

He then cites the cases of Tripiier, Kaposi, Reichel, Shepherd and Watson, and added: "Some of the cures have followed persistent recurrence after operation." In the dermatological literature there is a considerable list of spontaneous cures of cutaneous sarcomas.

Spontaneous recovery from choriocarcinoma belongs in a special category owing to the peculiar relations of this tumor. In 15 cases this process has been known to regress after the occurrence of pulmonary or vaginal metastases, in three of which neither uterus nor vaginal nodules were removed. In seven other cases recovery followed partial removal.

The spontaneous disappearance of multiple implantations of abdominal tumors has been recorded by many authors. These cases have been reviewed by Taylor and Alsop (1932), who add five cases of their own. They find that the regression occurs with papillary adenocarcinomas of ovary, especially in young subjects, endometriosis and pseudomyxoma. In many cases a partial removal of the tumor was accomplished at operation.

He then discusses cases of breast cancer in which improvement or regression occurred apparently spontaneously, noting that in MacKay's case (1907) improvement was coincidental with absorption of pleural exudate, and added: "I have followed several very resistant cases which were marked by continuous ascites, sometimes chyloform." Hodenpyl (1910).

He then cites the two extensive catalogues of the cases of supposed spontaneous cures of malignant tumors reported in the literature by Lomer (1903) and Rohdenburg (1918). Ewing concluded: "With very few exceptions these cases fail to furnish satisfactory evidence that an established malignant tumor actually did disappear spontaneously. Some event usually happens which may account for the disappearance of the tumor. Rohdenburg finds that this event is usually an incomplete surgical operation or some rather severe febrile disturbance." (Ewing, 1940).

Self Healing Epitheliomas

Charteris (1943) reported on five cases of multiple self healing epitheliomata occurring in a family in Scotland: The patient, his father and three of his five sons. Finally the patient died of rapid and extensive recurrence of his anal lesion, at the age of 72, nearly 50 years after the first lesion appeared.

In discussing this case and those of the three sons who were similarly affected, Charteris noted: "Capacity for healing was obvious in all...for a certain time, as evidenced by the many scars, but it failed eventually in the case of the parent, and was feeble or absent in the case of the sons by the time they came under observation... Almost all the lesions appeared on the exposed surface of the body but there is no obvious physical or occupational cause to account for this except for the possibility

that normal ultraviolet radiation may play some part.

"All who deal with malignant tumors are aware of the very different grades of biological activity met with even in one class, as is well known in the case of carcinoma of the tongue, and they would probably agree that the body mechanisms of defense and healing play a part in modifying the course of tumor growth. This is seen to an exaggerated degree in such cases as have been described and so it is suggested that a more intimate study of these patients might be of some value. Increasing knowledge of defense and healing processes might carry with it possibilities of their artificial stimulation, and it is conceivable that this might be of value in the therapeutic field." (Charteris, 1951)

Spontaneous Regression

Huth (1952) made a detailed analysis of spontaneous regression and remission in leukemias and cancer. He asks whether from the clinical observation of spontaneous remissions a plan of treatment could be developed. He states that this question was first asked by Busch in 1866, and then later by Lassar, Fehleisen, Coley and others. All of these used methods available at their time. Huth, therefore, proposed to investigate this question in the light of modern research.

Spontaneous remissions were mainly observed in skin cancer. All authors denied that this was really completely spontaneous without some outside help, but believed that there is a possibility of partial spontaneity; e.g., M.B. Schmidt (1903) and Ceelen described destruction of embolic lung metastases. Borst assumed that cells circulating in the blood were continuously destroyed. Konjetzny (1918) observed destruction in the omentum of metastases from gastric cancer. Therefore, it seems that there are powers of resistance to cancer in the body, but they are rare. Sauerbruch (1922) believed that spontaneous cures may occur.

The author would like to call "spontaneous cure" only those where cancer regressed without medical help, or without the occurrence at the same time of another illness. Remission after purulent diseases, he would like to call "Naturheilung."

1. Analysis of Remissions of Leukemias.

A case of remission of leukemia observed by the author prompted this paper. Smith and Bell stated that remissions in acute leukemias occur in 2 to 3%. Huth saw only one in 101 cases. As folic acid antagonists cause remissions in a third of the treated cases, according to Dameshek, only those cases are considered which did not receive folic acid antagonists. However, such remissions last only for three months. As causes of remissions, he enumerates from 67 cases the following:

- (1) Arsenic. (2) Phosphorus and other radioactive isotopes. (3) Urethane.
- (4) Blood transfusion, including exchange transfusions. (5) Bone marrow extracts.
- (6) Yeast adenylic acid. (7) Infections with certain organisms, especially erysipelas, or pyogenic infections. (8) No cause for remission found.

The author believes that the first three have only palliative importance in treatment and therefore are the same as (8). Blood transfusions cause remissions only occasionally. They last only two to three weeks. Repeated exchange transfusions become less and less effective. (5) Bone marrow seems to cause some remissions. (6) Adenylic acid made from yeast, only one case known. Possibility that cause was not adenylic acid but impurities from yeast (micro-organisms). (7) Infections: 30% of all remissions are caused by erysipelas, purulent infections or infections in which large amounts of bacteria are destroyed.

Huth then described a case of Henning's (1936) who observed that when myelogenous leukemia was treated by intramuscular injections, and that when abscesses occurred (*Staphylococcus aureus*), remissions of leukemia occurred. Similar case described by Moeschlin (1944): Another case described by Von Bock (1932): (Infection with hemolytic streptococci). Remission started after three weeks and lasted for three months. The patient died of bronchopneumonia. Autopsy showed many bacteria in the alveoli of the lungs, but no sign of host resistance. Huth concludes that therefore remission does not only demand invading bacilli, but also lysis of bacteria by the resisting body: In other words, pus is necessary. For the same reason, he believes that the stimulation of the reticulo-endothelial system by bacteria cannot be the

important part of remission. Glanzmann (1942) described a case of pus formation with staphylococci. Other cases were described following erysipelas, pneumonia, sepsis-- always infections which were connected with lysis of bacteria. Huth's case was caused by a staphylococcal infection. Huth believes that lysis is important, he believes that rare remissions are caused by the fact that the body is no longer able to form pus. He thinks that in more advanced cases this could be initiated by "giving infection plus blood transfusions."

Some authors believe that in a leukemic patient, something is missing which helps the body develop megaloblasts into normal leukocytes, just as in pernicious anemia patients something is missing which helps the body develop erythroblasts, into normoblasts. Blood transfusions help for some time to provide this material and as a consequence leukemia improves for some time.

II. Analysis of Spontaneous Cures of Sarcoma and Carcinoma.

Huth does not claim to be complete in his cases. His charts contain 26 sarcomas which reacted to erysipelas, and 32 carcinomas. He intentionally did not discuss spontaneous remissions of unknown origin. Beside erysipelas, he mentions as possible chemical materials which caused remissions: (beside those mentioned under leukemia) N-Lost, Stilbamidine, carcinogene "Kohlenwasserstoff," T.E.M. and x-rays. He also mentions hormonal materials in cancers of genital origin. But he thinks that none of these materials cure cancer. As to initiation of remission "by nature," he mentions the case of Busch: In the summer of 1869, a 19 year old girl was admitted to University Clinic of the University of Bonn, Germany, suffering from a tremendous sarcoma of the cervical lymph nodes. As rapid death was expected, a trial was made to induce erysipelas artificially. There was an "airy beautiful ward" in the clinic where there was a corner into which no patient with an open wound was permitted to be laid. The reason was the experience that every patient in this corner became infected with wound infection, but not the patients in the other beds. Our patient was put into this corner and a wound was created on the back of her neck by cauterization (burning). The patient developed a first degree burn and after one week, erysipelas developed from this burn. Fever was never higher than 106°F., and pulse never above

120. The sarcoma became softer immediately and measurements of the circumference of the neck between the 8th and 12th day revealed decrease in size of about 1 cm. a day. At the end of the second week, the tumor at the back of the neck had entirely disappeared, and the skin looked wrinkled. The main mass had reduced to the size of an apple and could be easily moved towards the skin and underlying tissue. However, at this time the pulse became almost imperceptible and at times the pulse beat stopped and the patient became pale. There was also a feeling of "precordial anxiety." Temperature became lower than 30°C., and it was assumed that the rapidly deteriorating tumor mass was absorbed by the blood." The author feels that this case of Busch is typical of the possible effect of erysipelas on tumors and also of the danger involved in such treatment.

Bruns subsequently reported three cases, and Coley reported three further cases (all sarcoma). Eschweiler found an additional seven cases and Wolfsheim another six. The last named series contained two carcinomas of the breast observed by Czerny. Fehleisen was the first physician to induce erysipelas artificially, and R. Koch and Petruschky reviewed the results and concluded that the "therapeutic influence of repeated streptococcus infection on the course of cancer cannot be denied."

Huth also mentions a case of Weichel in which erysipelas cured penile cancer. At autopsy no signs of the tumor remained. In several cases where erysipelas was artificially induced the infection proved fatal, as described by Bruns. Nevertheless, Bruns felt that the method was justified in cases of inoperable cancer.

III. Results of Analysis in Leukemia and Malignant Tumors. Questions for Experiments.

1. Comparing results in leukemia with those in malignant tumors, a surprising similarity of effective factors is found.

2. In spite of the fact that leukemias, sarcomas and carcinomas are all malignant tumors, there is a different grade of virulence. No complete cures of leukemias are known; however, there are some known of sarcomas. Carcinomas stand in the middle. In other words, "virulence" may be ordered in the following order: sarcomas, carcinomas, leukemias.

3. Cures and remissions occur spontaneously only if there is a greater collection of pus in the body or after erysipelas. No matter whether in the skin or lungs, a lysis of the causative organism occurs. This lysis is the decisive factor. Fever by injection of heat-resistant bacterial toxins is without effect. (Comment: this is incorrect, see Fowler and Miller and Nauts 1953-1970). The cure, however, is not tied to any specific bacillus. According to clinical observation, cure is caused by staphylococci and pneumococci. The effective materials from these organisms should not be confused with toxins liberated in vivo, as Coley assumed, as never was a remission observed when the body was flooded with toxins and the causative organisms without any ^{host} ~~strength of~~ resistance within the affected body. The curative effect may only be observed if the effective endotoxins of cocci are liberated in solvent form or are liberated tied to corpuscles.

4. What are the differences between the tumor bearing cells and the bacilli which cause purulence after having invaded the body? Many experiments show that there are decisive differences between the cells of an individual who acquired malignancy spontaneously and healthy persons (e.g., the experiments of Hackmann with immunization of mice which acquired tumors spontaneously). Malignant degeneration is an illness of the whole body. What may be the nature of this malignant degeneration is an unsolved question.

For an experiment with animals, it is important to initiate the lysis of cocci as it occurs in pus, and to isolate the effective material. This will prove then whether the working theory derived from clinical observation is correct or incorrect.

5. It should be noted that deaths have occurred after the rapid degeneration of malignant tumors under erysipelas, and that Jacobsen had similar results from animal experiments.

6. It should also be discussed whether the irritation caused by the infection alone causes the remission of malignancies. This seemed to be the case in the method originally devised by Coley: Coley evolved the theory that during erysipelas, the toxins developed by the streptococci harmed the cancer cells. However, with the toxins

of streptococci alone, Coley did not achieve the same successes observed in erysipelas, which suggests the possibility that the effective materials were not contained in his vaccine. Best results were obtained by sterilization, in which the bodies of streptococci and *Bacillus prodigiosus* were killed at 56° , or, in other words, still contained the bodies of these bacilli. This compares with the results of Roskin and his collaborators who formed a lysate by lysis of *Trypanosoma cruzi*, which was slightly toxic but very effective against tumors formed by transplantation. Finally, Lewisohn cured 30% of mammary carcinomas of mice with the extract of spleen from mice. However, this extract had to come from mice in which transplanted sarcoma 180 had been cured by spleen extract from beef.

The author would like to assume that irritation by infection plays a role, but that beyond this, a definite chemical compound is effective.

7. As for animal experiments, how does an infection occurring remote from the tumor have any effect on this tumor? The infection must be controlled in order to prevent the death of the animal. It must cause enough pus. Many organisms should be examined, including yeasts and molds. Above all, an organism should be looked for which is effective against tumors but is not unduly toxic. Tests for this purpose are essential. Laszlo developed a method of experimentation for Sarcoma 180 in mice. He excised the tumors after injection of the substance which was to be tested and compared the weight and size with another case, which originally was the same size and weight. There are disadvantages to this method because transient remissions occur and the cell changes during remission may not be sufficiently observed. However, ascites carcinoma of mice offers itself as an ideal object for experimentation.

In his animal experiments, Huth followed the methods of Lettré and Klein. The advantage is that spontaneous remissions were never observed and that tumors may be formed in 100% of cases. Cell material may be obtained by puncture at any time without interrupting the development inside the mice. By weighing the living animal conclusions may also be drawn. However, such experiments require controls (spontaneous cancer of mice) before they can be applied to human beings.

IV. Experiments with Animals.

1. Experiments with ascites carcinoma of mice.

(a) In vitro: Suspension of adenocarcinoma (Caspari) with *Oidium albicans* (the thrush fungus) caused complete lysis of carcinoma cells after 24 hours at 37°C.

Under the same conditions, no lysis occurred of normal liver cells. The *oidium* strains used had to be stimulated by passing through animals or by growing on blood-yeast plates.

(b) In vivo: In 1911 M. Beck observed that if he injected *Staphylococcus aureus* killed 24 hours previously at 100°C. directly into the tumors in mice, the tumors regressed completely. This did not occur if he injected it subcutaneously remote from the tumors.

In Huth's own series, he injected *Oidium albicans* into peritoneal cavity of mice suffering from Ehrlich ascites carcinoma. Shortly after injection, *Oidium* was phagotized by invading leukocytes. Cancer cells remained untouched. If, therefore, a large amount of *Oidium* was injected, ascites tumors became necrotic, but the toxic effect was so strong that all the mice died.

Penicillium notatum had similar results. This fungus was not as toxic as *Oidium albicans* to the general health of the mice. Therefore, higher dosages could be used.

Then the author examined the effect of subcutaneous injections remote from the tumor:

(1) as it was known from clinical trial that penicillin does not limit the lysis of carcinoma by *Staphylococcus aureus*, a suspension of these cocci in penicillin was produced and injected. Cancer improved, but the animals died as high dosages of the staphylococci were necessary.

(2) *Oidium albicans* was also effective and less toxic than staphylococci.

(3) *Penicillium notatum* was also effective and even less toxic than *Oidium albicans*.

Huth then discussed the morphological changes which occur in cancer cells during lysis after treatment with *Penicillium notatum*. He states that probably basophile material in yeast products is responsible for growth. He then discusses the importance

of ribonucleic acid. The site of this ribonucleic acid and its action is found in the chromosomes of the protoplasm. He also mentions the fact that carcinogenic chemicals like benzpyrene are mainly accumulated in these chromosomes. As to penicillin, he states that the purified salts of penicillin used in chemotherapy have no effect. However, there are authors who feel that penicillin has some effect on cancer and aureomycin on leukemia.

2. Experiments on the Spontaneous Cancer of Mice

Subcutaneous injections remote from the tumor were used. Injections were toxic and the animals died, but with *Oldium*, regression of tumors was found. The same is true with *Penicillium notatum* (with less toxicity). (Huth, 1952)

Stewart (1952) stated: "Pathology has never found a definition for cancer. To define it requires condensation and simplification of many attributes that contribute to the knowledge of an entity. These attributes expand or contract as data concerning them increases. Until such time when some great generalization becomes possible, the expansion of data seemingly creates spreading confusion.

"Every medical student is furnished with a definition of cancer, usually one that merely emphasizes one supposed attribute of the process modified by one or two adjectives. Thus, Ewing defines a tumor as follows: 'A tumor is an autonomous new growth of tissue.' This statement appeared in the first edition of Neoplastic Diseases in 1918. In the last major textbook of pathology to appear in this country this definition is given again, although very slightly modified: 'A neoplasm is an uncontrolled new growth of tissue.' These two definitions vary in the matter of two adjectives - 'autonomous' and 'uncontrolled'. Autonomous means existing independently or responding or reacting independently of the whole. In the field of biology there is no such thing as autonomy, and 'uncontrolledness' - if I may coin a word - is an equally unacceptable concept. Because biology has failed to discover laws of tumor control, it has no right to assume that they do not exist. Actually, investigative medicine is forced to admit that they do exist; for if they did not, cancer research in turn should not exist, because it could have no future. Thus the mere existence of research constitutes a denial of the definition of cancer."

Better than the words 'autonomous' and 'uncontrolled' might be the adjective 'heterotopic', which refers to the ability acquired by the tumor cell to exist outside of its locus of origin. The skeptic would, of course, say immediately: "How about carcinoma in situ, where the tumor cell is still within - let us say - the mucous membrane of origin?" This is not really an objection, because even while within the germinal layer of the epithelium of origin, the tumor cell looks like a cell apart. Further, as it moves toward the surface, it becomes heterotopic, because the immature-looking tumor cell is heterotopic as soon as it leaves the environment of the germinal layer. It is obviously heterotopic within the tissue of origin as soon as it leaves the immediate environment of the cells of origin, whether

or not it remains within the organ. Be that as it may, little satisfaction can be obtained by quibbling about definitions for actually there is no definition of cancer that cannot be attacked.

Carcinoma in situ

By definition, a carcinoma in situ is a neoplastic entity wherein the tumor cells still lie within the epithelium of origin. We accept the fact that they are cancer cells because, when they leave this site of origin and infiltrate or disseminate, their appearance is that of the cells still resident within the site of origin. This similarity is the only thing we have to identify them as cancer cells. Hence, in our present state of knowledge, they are cancer cells.

There is abundant evidence that these cancer cells may have remained within this site of origin for ten years or longer. This extensive period of relative quiescence, although most commonly recognized in the uterine cervix, is by no means thus restricted. It can be observed in in situ malignant cervical lesions, laryngeal cancer, glandular cancers of the endometrium, lobular carcinomas of the breast, and perhaps other neoplasms. Chronology can be established only by fortunate accident in such cases. Thus, in a biopsy report of in situ cancer of the larynx occurring many years ago, the clinician doubted the report of carcinoma and did nothing. Infiltrating carcinoma first became apparent seven years later.

Recently, a patient was admitted to a certain clinic under the diagnosis of mammary carcinoma arising in the scar of excision of a benign lesion. The benign lesion had been removed a decade before. The infiltrating cancer was of the lobular pattern. Fortunately, the sections of the old benign lesion were available for re-examination, which revealed lobular carcinoma.

The chronology of the endometrial cancers was well established by Hertig. He re-examined curetted materials taken at various intervals prior to the curettage that demonstrated unmistakable cancer. I do not wish to infer that this slow evolution is a feature of all cancer development; if such were the case, we would have no means of proving it. Rather, I suspect it to be a feature of some examples of many types of cancer, and a feature common rather than rare. I do suggest that

slow evolution is evidence of control.

Every cancer must begin as a cancer in situ - although this term is popularly applied to one anatomic type, cancer of the cervix. It may be equally applied to many mammary cancers, not alone the in situ lobular carcinomas, but also the papillary cancers of ducts that fail to infiltrate. The term is suited to describe certain bronchus cancers, many early cancers in rectal polyps, some gastric cancers, some endometrial growths, and would have a much wider application if we only saw more early lesions.

In these in situ stages there is evidence of cancer control. In the epidermoid cancer the tumor cells respect the basement membrane; instead of infiltrating and destroying it, they move outward toward the layer that normally desquamates - thus following the course normally assumed by the noncancerous cell. When the tumor cells extend inward, they first fail to infiltrate, and only progressively replace the linings of pre-existing gland ducts. In other words, they exhibit a certain property of tissue interrelationship that fails to depart in any essential from that exhibited by the normal cell.

In an in situ gastric cancer, the cancer cell seems liable to necrosis and erosion; but the regenerating cancer cells, instead of infiltrating, regenerate to replace the lost surface. Therefore, the in situ gastric cancer may be confused clinically with a peptic ulcer, because it heals over eroded areas under dietary regime and thereby lends a false sense of security. Thus, the normal attribute of healing effort is shown - a sort of normal physiologic behavior, rather than the much touted 'autonomy' and 'uncontrolledness'. Later on, when some attribute or attributes are added to behavior, more characteristic features of neoplasia appear, rendering the totally unbiological word 'abnormal' more appropriate.

In some instances of in situ epidermoid carcinoma of the uterine cervix, positive smears have been obtained repeatedly. Then, quite suddenly the tumor cells cease to appear. If we assume such cases do represent early cancer - and we are relatively certain they do - then we must admit that the normal process of desquamation rids the mucosa of its tumor. Further, the stimulus to further production

of tumor cells ceases. In but one instance have I had reason to believe that a fully developed cervix cancer had disappeared. This was in 1946 in a patient with incontrovertible biopsy proof of cervical carcinoma, which had developed beyond the simple in situ stage. This patient has no cancer today. Furthermore, she had had no treatment unless it be said that the securing of a very small biopsy not more than 2 mm. across had removed the cancer. This idea is conceivable but extremely improbable.

There are curious features about these in situ cervix cancers in Jewish women that interest me greatly. At my request, our statistics department investigated the incidence of cervix cancer in a four-year period. There were 702 cases and of these but 26 were in Jewish women (3.7%). The total hospital population is at least one third Jewish. In the detection clinic, however, about one fourth of the carcinomas in situ were in Jewish women. Yet, the frequency of these tumors in all women examined was the same as known incidence rates of cervical carcinoma. Unless there is some discrepancy in the data, which, of course, there may be, the impression is that such lesions in Jewish women disappear. Or it might be that their total evolution is so slow that they do not contribute their full bearing on the frequency of developed cervix cancer. Are we all wrong in regarding these in situ lesions as cancers? This I doubt. Are there racial behavioristics? This one must question because there is no such thing any more as a Jewish race. Thus, the matter remains unanswered. More data are required with larger figures.

"I believe that the diagnosis of in situ cancer of the cervix is made too frequently. There are dyskaryoses to be seen in pregnancy and in trichomonas vaginitis that are very confusing and are being called cancer. I do not think pathologists are well aware of this pitfall.

"Recently, I was talking with Dr. TeLinde, chief of gynecology at Hopkins. I asked him about the diagnosis of in situ cancer of the cervix in pregnancy, and he said he did not dare make it. I asked him what he would call the same type of cytologic change in a middle-aged nonpregnant woman, and he said he would call it in situ carcinoma. I am in complete accord with this point of view, but it opens more

problems than it solves. Why are two lesions essentially identical in pattern different in different physiologic states? Are they both cancers? Do they represent processes that are usually considered irreversible; and is one reversible, though cancerous, by 'normal' means? In other words, is it spontaneously controllable? If it is, then have we not a lead toward the controllability of the other process that does not occur in pregnancy? Have we a lead on causation?

Spontaneous Control

"Spontaneous or induced cancer control is evidenced in certain tissue reactions of the host. In one variety of cancer of the breast a tremendous lymphoid infiltrate occurs. In fact, for this type we have invented the term 'medullary carcinoma with lymphoid infiltrate'. The prognosis with this type of cancer is much better than with any other type of infiltrating mammary carcinoma, even though nodes are involved. We believe this massive infiltrate indicative of a state of spontaneous host resistance. As an example of what we might call induced resistance, I refer you to certain observations we have made on cervix cancer treated by external radiation via vaginal cones. When a patient has a cancer of the cervix that is partly in situ and partly infiltrative and when one treats this patient by x-ray through vaginal cone and studies the result pathologically, it will be seen that the in situ portion will persist whereas the adjacent superficially infiltrative portion will show very advanced degenerative changes directed toward disappearance. Since differences in dosage cannot be significant within areas of no more than one or two millimeters, we have to assume that the difference of behavior is due to the fact that the cancer that has infiltrated is in the presence of a reactive bed. Further, we assume that the effect of the radiation has been sufficient on the tumor cells so that the forces of the reactive bed, whatever they are, become manifested. Thus the body is not accepting the tumor cell passively, at least in this stage. Unfortunately, the other extreme also exists in the cancer field where the acme of tumor acceptance is seen. This is best illustrated in advanced disease where, as in a recent case reported by Dargeon et al., transfer of melanoma occurred from mother to fetus, resulting in death of the infant in early life.

The Influence of Hormones

"The field of prostatic cancer is curiously contradictory. In the last decade or so it has been widely admitted that some 25% or more elderly subjects had miniature prostatic cancers. Since it is apparent that these have not behaved like clinical cancers, one is justified in assuming that they are restrained by some sort of physiologic control for long periods. We have no knowledge of wherein this control lies. However, not only in these miniature cancers but also in clinically fully developed prostatic cancer, I have sometimes noted cytologic patterns suggestive of those seen in the prostates of therapeutically castrated and estrogen-treated individuals. Therefore, it may well be that spontaneous alterations of hormone environment may be invoked in explaining this long evolution or restrained activity.

"This attitude is reinforced when one examines the incidence curve of clinically detected breast cancer. This curve shows a double peak. It is rising prior to the menopause, then it falls, and then it rises again. This information, coupled with the knowledge that certain mammary cancers are favorably influenced by an altered hormone environment, suggests that the menopause provides a changed hormonal environment unfavorable to the progress of certain mammary cancers. Therefore, the clinical appearance of some breast cancers is slowed. Had no change in environment occurred, the lesions would have progressed at a normal rate and eliminated the slump in the incidence curve.

"We know that prostate cancer exhibits regressive alteration after castration or hormonal therapy and that breast cancer also does. Therefore, remembering the long latency periods sometimes involved in these diseases, may we not be justified in believing that some lesions in these organs, which ordinarily would progress, may involute completely? We have no evidence from the prostate that such is so. In the breast, however, it is quite certain that papillary lesions of ducts which are capable of giving rise to breast cancer do show, at times, very pronounced involutional patterns tending toward atrophy and fibrosis. The fact that some would deny that such lesions can pass over into cancer does not disturb me, because no one who has seen a large amount of breast material would deny that they do. Then if we admit

that there are levels in the development of these lesions where one could not be certain whether the cells one sees are cancerous or not, is not one by inference justified in assuming that some small early breast cancers disappear spontaneously? This evidence, in turn, would seem to indicate that we are witnessing control.

"It may be said that these are specific examples and that such phenomena cannot exist in other parts of the cancer field. However, no one knows that such is a fact. Because we do not know of controls, we have no right to assume their non-existence. We see evidences of control only in those situations where we have learned something about the modifications of environment possible. Our status is like that of embryology prior to Spemann's classic demonstration of organizers. Certain patterns of tumor growth are close duplications of stages of embryonic development, developmental patterns that mature under control. Let me cite for you an example. Two microscopically similar tumors exist, one in the testis and one in the ovary. The first is commonly called seminoma, the second dysgerminoma. Some months ago I received a section of ovary from a fetus. I looked at it and said it was a prenatal dysgerminoma. Another pathologist, who had not forgotten his embryology, said the material was only cords of early sex cells. After he said that, I secured a number of ovaries from embryos. Sure enough, at a certain embryonic age I could have thought that every ovary contained dysgerminoma. Yet, naturally they couldn't have been tumors. Instead, they would have undergone normal maturation as they fitted into the pattern of organization of the host. Still, seen in a young adult, they would have constituted a tumor.

"Just what is a placenta? In certain stages an early placenta looks like a malignant choriocarcinoma. Furthermore, it acts like a cancer. It invades and destroys the uterine wall and derives its blood supply from curious lakes of blood without formed vessels. Its cells are large and atypical. Remnants of placental cells break off and exist temporarily in such organs as the lungs, and then they regress. Sometimes, as in the case of what one calls chorioadenoma destruens, the process becomes even more cancerlike in clinical behavior, only to regress. The diagnosis is exceedingly difficult for the pathologist, and obviously many cases of

cured choriocarcinoma reported were never real choriocarcinomas at all. Every early placenta looks and, for a period, acts like a cancer. I like to think of it as a cancer, in the high proportion of cases under control. If we don't think of it as a cancer, we have to abandon the microscopic criteria for the diagnosis of cancer - something I am not willing to do.

Spontaneous Regressions

"Striking evidence for the state of control appears in the admittedly rare instances of spontaneous regressions of established cancer with proved metastases. I say 'spontaneous' although naturally these instances are not examples of tumor disappearance in the absence of all treatment, but involve therapeutic procedures either insufficient to cure disease or not even directed to the site of disease. I wish to give you examples. In all but one case I have myself seen the pathological material. In the instance where I did not see it, the exploratory surgery was performed by Dr. Allen O. Whipple. The pathologic study of this case was made at Presbyterian.

"The first case I saw was one of uterine myosarcoma treated by Dr. George Pack. The tumor was wholly inoperable, being spread throughout the pelvis and in the mesenteries. The lesion was soft, very vascular, and hemorrhagic. After biopsy was performed, the patient was treated by a radium bomb. As might have been expected, nothing happened. There was no evidence of any radiosensitivity, and the mass failed to regress at all. Then just before the completion of treatment and within the course of almost hours, a dramatic change occurred. The patient developed a high fever, an urticarial rash, a high eosinophilia, and within a few days lost kilos of tumor and ascitic fluid. The tumor completely disappeared; and when last I heard 10 years later, the patient was well. Five years or so after treatment, she had some insignificant lesion of the cervix for which she received a small amount of radium. She repeated the hypersensitive reaction. What I assume happened was that some alteration occurred in the tumor protein of this patient and she became sensitized to her own protein. This, in turn, provoked an intense immune reaction. Certainly this cancer came under biologic 'control'.

"The next case was in an infant a few months old. He was brought to the hospital with multiple tiny subcutaneous nodules. When one was subjected to biopsy, a diagnosis of neuroblastoma was made. After the final result I sent these sections to various pathologists in New York and Boston and always got back the same diagnosis: neuroblastoma. The child had small radium plaques applied to one or two of the nodules to see if they exhibited enough sensitivity to warrant, let us say, general body irradiation. They did not. He also had a little of the old Coley toxin - not really treatment. After being discharged with a hopeless prognosis, the nodules proceeded to disappear. Today, more than five years later, he is a perfectly healthy child. Here no known allergic reaction took place.

"Back in 1937, I saw another case of metastatic neuroblastoma in a young infant, this time producing a destructive metastasis in the upper end of the left femur. We have to say it was a metastasis, because we have no reason to expect a neuroblastic tumor primary in a bone of the lower extremity. This child was treated by x-ray directed in adequate doses to the involved femur. Treatment was directed to the metastases and not the primary, which probably was retroperitoneal if it was in the usual spot for these tumors. This child is now 14 years old and has no trace of tumor. The primary must have been under control, perhaps through some spontaneous maturation - such as was described years before by the late Harvey Cushing in a slightly similar situation. Only two months ago I received follow-up data on this case. Again I examined the biopsy material and could arrive at no other diagnosis than that originally rendered." Comment: This patient described by Wolbach and Cushing (1927) received Coley toxins alone for two years. His recovery is now regarded as being due to this treatment. He remained well in 1970, 59 years after onset. (Fowler, 1970)

"At this time, I saw the initial x-rays on this last case and took them to our department of roentgenology. There, I was happy to receive uncoached a report that the lesion was consistent with metastatic neuroblastoma. The doubter will, of course, say perhaps these were not tumors. Perhaps embryonic neuroblasts disseminate to such sites as skin and bone and vanish in the course of normal maturation. However,

I have to say that these neuroblasts look microscopically like tumor; they grow and destroy; they are heterotopic in location; and hence they fulfill the definition of cancer. Wyatt and Farber describe a cure of neuroblastoma differentiating into its adult counterpart after incomplete surgery.

I am indebted to Dr. John Godwin of the Ochsner Clinic for still another example of extreme regression of neuroblastoma in infancy. At birth the infant's abdomen was enlarged. No increase in this enlargement was observed by the parent during the first month of life. But at the end of that month, there were noted multiple subcutaneous nodules 2 to 4 cm. in diameter scattered over the abdomen, groins, back and head. These were large enough to produce bluish discoloration of the skin. When admitted to the Clinic, the cutaneous nodules were noted, and in addition the abdomen was markedly protuberant and tense. A large mass occupied the region of costal margin to iliac crest on the right. It extended 5 cm. over toward the opposite side at the level of the umbilicus. Excretory urograms showed both kidneys displaced downward, and the right pushed medially until its ureter lay in the midline of the abdomen. Biopsy of the cutaneous nodules (2) showed neuroblastoma, which diagnosis I have confirmed beyond any question. The only treatment administered was a little nitrogen mustard over a 4-day period, and this had no immediate effect whatever during a month of observation. Then, six weeks after discharge, the abdomen began to shrink and the cutaneous lesions started to disappear. On re-admission to the clinic about seven months after first admission, the child appeared like a healthy infant. Only two cutaneous nodules could be located. The liver edge was palpable three fingers below the right costal margin, which does not indicate any great enlargement. Excretory urograms showed the kidneys still low, but the previously displaced right kidney in a much more normal position. The original mass was much smaller. I do not maintain that this child will be cured, and in fact just yesterday learned that new cutaneous nodules have appeared. However, the fact that this mass regressed enormously late after treatment and in a fashion that could not well be related chronologically to treatment reinforces my belief that these other cases are true examples of spontaneous regression of neuroblastoma. (Comment: This

child had concurrent infections and is included in the infection series in Fowler's monograph on neuroblastoma (1970). She is entirely well in 1970, 20 years after onset.)

"And while thinking of tumors of children, it may not be impertinent to recall the bulky hypertrophic angiomas of infancy, often miscalled sarcomas by the uninitediated. These tumors used to be treated vigorously by x-ray, radium, sclerosing agents, before it was realized that their tendency was to spontaneous disappearance, the local circulatory apparatus becoming 'organized'.

"No clinician who treats many examples of acute leukemia - usually defined as a malignant tumor of the marrow - is without these curious examples of profound remissions of the disease. When this happens, the peripheral blood returns essentially to normal status, sometimes for a considerable period.

"Recently, I saw a node from a patient who had Hodgkin's disease. Over a decade before Dr. Roy Kracke, one of the best known American hematologists, had made a diagnosis of leukemia on this patient, but the leukemia had vanished. Perhaps it was infectious mononucleosis, and unfortunately, Kracke is not alive to defend his diagnosis; but I do not see reasons to doubt him.

"To one who witnesses the temporary disappearance of large leukemic masses under ACTH, transient though these disappearances are, 'control' is an obvious feature of this tumor. Only the why and the how are great problems. In certain examples of lymphosarcoma, a history is obtained showing repeated enlargement and regression of nodes prior to the establishment of clinical stability of the disease. Unfortunately, we do not know just what such nodes show pathologically - that is, whether they are at that stage lymphomatous.

"The case of controlled cancer observed by Dr. Whipple was in a nurse. She was explored and found to have a large, inoperable malignant hepatoma. Instead of dying of the disease in a relatively brief period, she survived in apparent health for some twelve years, finally dying an accidental death. Autopsy revealed a small, shrunken lesion completely fibrotic and with only traces of atrophied tumor cells.

"In the old days, there were a few strange events in patients treated with the old Coley toxins. It is generally presumed that the effect of toxins was from hemorrhages induced in the tumors. Yet, I seriously question whether multiple hemorrhages can themselves be responsible for the disappearance of large masses of involvement, even though one might invoke this explanation for the destruction of small microscopic deposits. Let me cite an example. A man had amputation of a lower extremity through the lower femur for primary reticulum cell sarcoma of bone. Disease recurred the entire length of the remaining femur. A metastasis occurred in the skin of the abdominal wall. This was excised and its character proven. All disease vanished under Coley toxins alone (Miller & Nicholson, 1970, Series A, Case 3) and the patient is still well now after 30 years. I don't think the result was from hemorrhages in the tumor. Hemorrhages always leave peripheral viable tumor cells. The only exception to this rule is the very rare minute testis tumor that produces metastases, but where the primary through spontaneous hemorrhage is reduced to a small scar without residue. This occurs in testicular choriocarcinoma and in seminoma, although in the former the residue of nonmalignant teratoid element may persist. In the Coley toxin cases, I like to think that some combination of toxin and tumor protein has occurred and made the tumor antigenic, but naturally one lacks all proof.

"The whole field of metastatic cancer is riddled with examples of growth control. Every late metastasis is an example of control. When a successfully resected rectal cancer reappears, let us say, in the thyroid as I have seen it do more than once after as long as seven years, or when a breast tumor or a melanoma first exhibit metastases after 20 years, are we not justified in assuming a long interval of control of growth? If we knew wherein this control existed, we would have gone a long way toward the answer to cancer.

"One of the most striking examples of what we may call latent metastasis appeared quite recently. The patient was a woman aged 55. She first entered Memorial complaining of shortness of breath. She expired 11 months later from the effect of her tumor. The point is that this tumor was a type of ovarian cancer, and the involved ovary had been removed 35 years before her first admission to Memorial.

Other examples of long latency with this type of tumor exists, but this is the longest to my knowledge. At autopsy there were good and sufficient reasons histologically for this long course. The tumor varied greatly from area to area - in some areas being actively proliferating, in others atrophic-looking, degenerate, sclerotic, and with the calcific deposits that commonly characterize the lesions naked, without their cuffs of tumor cells. To be sure, this tumor was growing. However, at the same time it was disappearing, even though the ultimately attained balance was in favor of the tumor rather than the patient. A similar case at the New York Hospital had a duration of 33 years.

"I suppose the all-time record for behavior of cancer is to be found in a case of cylindroma - or, if you prefer the term, adenoid cystic carcinoma - of the salivary gland that was first noted at the age of 15, was first operated at the age of 29, and killed at the age of 80.

"Thinking in the cancer field is perhaps too largely directed to methods of artificial destruction of the cancer cell - either by its radical removal or its chemical destruction. There has not been enough thought given to biological control by the host. Of course, the former is easy when the setting is favorable, and we lack all the knowledge to undertake the latter. Still, I am willing to predict that the solution will be the latter, and that it may not be too many decades away.

"In closing, I wish to emphasize that the cancer cell, though superficially anarchical, is not, nor can it be unbiological, just so long as it is part of a biologic host. Moreover, there are differences in the patterns of host acceptance amounting to evidence for host control. Therefore, one may not be too far out of line in suggesting that great profit may ensue by redirecting some of the efforts at destruction of tumor cells or their radical removal toward an understanding of host-tumor interrelation, an understanding that must precede any biologically-planned attack on the cancer problem. One's philosophy toward the cancer problem may be engendered by one's attitude; to him who sees mainly anarchy, the problem's outlook is surely bleak. But where one looks more optimistically and sees evidences to justify optimism by the absence of this much touted 'unbiologic' anarchy, then surely the ground for optimism has been attained. (Stewart, 1952)

Everson and Cole, beginning in 1956, published a series of reports on spontaneous regression of cancer, comprising more comprehensive studies than others. In 1966 their textbook on the subject was published containing abstracts of 176 cases in the world medical literature or obtained by personal communications with physicians. Over 50% of these cases occurred in four types of neoplasms: hypernephroma, neuroblastoma, malignant melanoma and choriocarcinoma. Others included bladder, soft tissue, bone, colon and rectum, ovary, testis and breast. These cases were grouped in chapters by the organ involved. Other chapters dealt with regression of benign tumors, delayed recurrence or metastases and a final summary and conclusions.

The existence of these cases, they concluded, supports the concept of biological control of cancer and reinforces the hope that a more satisfactory method of treatment than surgery and irradiation may be found in future years.

Spontaneous regression could entail any of several mechanisms they speculated, including endocrine factors, fever and acute infection, unusual sensitivity to usually inadequate therapy, (i.e. incomplete surgical removal), or allergic or immune reactions. They noted that several remissions occurred following acute febrile episodes. In this study they arbitrarily ruled out all cases reported prior to 1900.

Spencer (1942) reviewed the subject of tumor immunity, citing from this voluminous literature seven monographs: Tyzzer, 1916; Woglom, 1922 and 1929; Murphy, 1926; Caspari, 1929; Lumsden, 1931; and Clemmsen, 1938, which, taken as a whole, covered the essential knowledge of tumor immunity up to the time each was published. Woglom's second review had a bibliography of over 600 titles.

Most of this report was concerned with experimental work on animal tumor systems. He noted that in recent years the blood supply of the tumor had been considered as a cause of regression: thrombosis, then necrosis. Regressions have been noted following an acute febrile episode caused by pneumonia and other infections in which the viscosity of the blood and the amount of fibrinogen in the blood is changed.

Spencer then reviewed the work of DaFano and Murphy and his colleagues on the role of the lymphocyte in immunity and the view of those opposed to these studies. He gave 49 references.

Duran Reynals (1940) reported on the neutralization of tumor viruses by the blood of normal fowls of different ages.

The knowledge that wide individual variations of susceptibility to tumor viruses exist among normal chickens dates from the discovery of the tumors themselves by Peyton Rous (1910). Such variations were recognized as ranging from extreme susceptibility to complete resistance, and included those cases in which rapid growth was followed by regression and resistance to inoculation.

The first worker to approach the humoral aspects of the problem was Carrel (1925). His work established the existence in the blood of normal chickens of some suppressing factor for the Rous virus.

The study of naturally occurring antibody-like factors which exhibit a suppressing action on filterable viruses has so far received little attention. In Duran Reynals' studies a factor behaving to all intents and purposes like a natural antibody for the virus of the Rous sarcoma, has been found to be generally present in the blood of adult Plymouth Rock chickens, whereas it is but occasionally found in the blood of chicks. Analogous suppressing factors for the viruses of the Fuginami sarcoma and the Mill Hill₂ endothelioma were also found in the blood of adult fowls.

It has also been shown that the susceptibility of the chick, as compared to the chicken, to the Rous virus manifests itself by a constant response (tumor formation) to very small amounts of inoculum and by the development of larger tumors. A very small percentage of adult chickens are highly susceptible to the virus and these, like the chicks, show very little or no antibody in the blood, whereas those more resistant or totally resistant show such antibody in amounts directly proportional to their degree of resistance. The latter holds true also for the Fuginami and Mill Hill₂ viruses.

The results show that a humoral factor has a great influence in conditioning the infection induced by these tumor viruses, and suggest, but do not prove, that the responsible factor is a viral antibody.

Duran Reynals noted that since plasma from adult fowls is often used in the cultivation of viruses of tumors and other diseases, the question might be raised as

to whether different results might be obtained if chick serum were used. In this connection, he cited Ludford's observation that plasma suppressed the culture of the Fuginami virus in vitro.

Summary: Paralleling the growth and aging of the individual there develops in the blood of fowls an antibody-like factor endowed with the property of pronouncedly suppressing the effects of the viruses inducing the Rous and Fuginami sarcomas and the Mill Hill₂ endothelioma.

In the case of the Rous virus, the only one studied in this respect, the factor is rarely present in young chicks, but is to be found almost uniformly in adult chickens. In both groups its presence or absence or the extent to which it is found stands, as a rule, in an inverse relationship to the incidence of tumors after inoculation and to the rapidly growing of the induced tumors. The same has been found to hold true for adult chickens of differing susceptibility to the virus. Those developing slowly growing tumor or no tumors at all have a large amount of the antibody-like factor, while those developing more rapidly growing tumors have lesser amounts of neutralizing factor or none at all. (Duran Reynals, 1940)

Burmester at East Lansing, Michigan, U.S. Dept. of Agriculture (1957-58) found that a high percentage of chicks can be protected against lymphomatosis by inoculating mother hens with the killed viruses of the disease. The immunity, passed from mother to offspring, tides the chicks over their susceptible period until they develop their own immunity.

(1944)

on

Warren and Ehrenreich were one of the first to report multiple primaries. They studied 2,829 consecutive autopsies on cases of cancer performed at three hospitals in or near Boston from 1932 through 1943. In an earlier report (1932) Warren and Gates had reported on a series of 1,078 cases covering the period 1926 through 1931. The incidence of multiple primary malignant growths in the second series was almost double that of the first: 6.8% as against 3.7%. They believed this was a reflection of the current awareness as regards cancer, resulting in more complete histories and histologic examination of all tumors excised.

Their criteria: "Each of the tumors must present a definite picture of malignancy, each must be distinct, and the probability of one being a metastasis of the other must be excluded. Malignant tumors of the same organ or of symmetrical organs were included only if the clinical history and the gross and microscopic findings proved them to be independent." (i.e. only six cases of bilateral breast cancer were accepted out of a total of 10. All cases of bilateral ovarian cancer were excluded.)

"The study of contrasted synchronous and metachronous tumors might provide an approach to the further elucidation of individual susceptibility to tumor development. Unfortunately, it is not always possible to be sure that such a distinction, which is of necessity based on clinical symptoms and biopsies, corresponds to reality. Furthermore, it is difficult to know how much significance to attach to the intervals between the development of tumors. . . There is not much difference as far as information regarding heredity goes, and indeed, regarding susceptibility as well, as to whether the patient develops his two tumors five years apart, ten years apart, or practically simultaneously."

". . . It has been suggested that multiple malignant tumors constitute an indirect measure of the degree of intensity of malignancy or of the disposition to cancer in an individual. . . " Multiple malignant growths in themselves do not alter survival rates to any appreciable degree. . . The presence of numerous malignant tumors does not necessarily imply a worse prognosis. It seems unlikely that the degree of malignancy is related to multiplicity. . .

. . .Although there is some evidence that organ or tissue specificity with regard to the development of tumors may exist, the evidence is not conclusive. Conversely, there is nothing that suggests antagonism between tumors from different organs or tissue.

The organs most frequently involved in the group of 194 multiple tumors:

COLON: 95 malignant tumors in 69 patients.

SKIN: 44 malignant tumors in 34 patients.

BUCCAL CAVITY & PHARYNX: 34 malignant tumors in 30 patients.

STOMACH: 28 malignant tumors in 28 patients.

UTERUS & CERVIX: 23 malignant tumors in 22 patients.

Almost all studies of multiple malignant neoplasms show a high proportion of multiple cancers of the gastrointestinal tract. These are chiefly of the large bowel and may be related to polyposis, in which secondary malignant changes are so common. . .In a third of the cases of carcinoma of the large bowel, there was a second carcinoma in this location.

". . .Collision of tumors (i.e., the encounter of two malignant tumors or their metastases) is infrequent. . .only three instances of collision tumor out of 194 cases of multiple primary tumors. The first presented the encounter of two primary malignant growths in their site of origin; a renal cell carcinoma and a rhabdomyosarcoma in the left kidney. In the second, an epidermoid carcinoma of the bladder metastasized to a mucinous carcinoma of the rectum. In the third there was collision between the lung metastases of a carcinoma simplex of the breast and an adenocarcinoma of the pancreas.

The co-existence between multiple malignant tumors and benign tumors has been noted by many authors, but statistical data are not really available. Although no attempt was made to determine the incidence of benign growths in this series, it was noted that a number of cases showed a striking number of benign tumors involving several organs and systems. Case 60, 431 (Table II, C.) provides a good illustration. The patient who was 58 years old at the time of her death had three malig-

nant neoplasms (leiomyosarcoma of uterus, with lung metastases, adenocarcinoma of ovary with numerous metastases, and lymphatic leukemia) and five benign tumors (adenoma of islet of Langerhans, Hurthle-cell adenoma of thyroid, leiomyoma of stomach, embryonal cyst of kidney, and hemangioma of lip).

In 1932, Wilson and Maher discussed the statistical significance of the occurrence of multiple malignant growths and estimated the expected incidence to be five to six per thousand (based on the Massachusetts mortality rates for 1902, 1912, and 1920-1927, prepared by Dr. H.L. Lombard). In analyzing the first series, Warren and Gates used a table set up by Lombard and centering at the same year as the cancer autopsy series. The expected number of multiple malignant neoplasms in the series of 1,058 cancer autopsies, on the basis of two years' duration, was 10.5, whereas the actual number observed was 40.

Desaive and his co-workers based their statistical studies on the population of Liège, Belgium, from 1925 to 1934. The expected incidence of multiple malignant growths was calculated to be 6 per thousand. It is noteworthy that, working with two entirely different population samples, Wilson and Desaive found almost identical figures (5 to 6, and 6 per thousand, respectively).

In Warren and Ehrenreich's second series the observed incidence of multiple malignant tumors was 68 per thousand; on the basis of both series it was 60 per thousand. The expected incidence of multiple malignant neoplasms in the second series was 17; the observed incidence was 194, or 11 times the number expected if chance alone were a factor. They regarded this as a further confirmation of the existence in some persons of a susceptibility or predisposition to cancer.

The ultimate goal in the therapy of cancer is the permanent eradication of the neoplastic growth and recovery of the patient. When a cure is not possible, the goal is toward retardation of the growth, with prolongation of useful and comfortable life. If prolongation of life cannot be achieved, therapy is directed toward palliation of symptoms or signs of the disease.

"The distinction between procedures that may retard the progress of neoplasms and purely palliative measures is. . .difficult.

"Objective improvement and clinical remissions of (chronic myelogenous leukemia). . .are achieved with radiation. Statistical comparisons of groups of patients treated with radiation and those not so treated, however, fail to demonstrate significant prolongation of life in patients receiving radiation. . .

"Despite repeated statements to the effect that neoplastic disease is more malignant, i.e., kills faster, in young patients than in those of advanced years, definitive studies fail to substantiate this clinical impression."

Spontaneous Regression: "For practical purposes, the course of untreated cancer in man is one of steady inexorable growth, spread and fatal termination. . .

The progression of growth in fully developed neoplasms is by no means uniform in all patients. Fluctuations in growth, occasional decreases in the size of the masses, necrosis and hemorrhage. . .and partial clinical improvement for varying periods of time are infrequent but not rare clinical occurrences. In the lymphoma group of neoplasms, temporary and partial remissions without therapy are seen in up to 10 per cent of the cases."

Even complete regressions of fully developed cancer, without recurrence and without therapy, have been recorded. . .(Rohdenburg, 1918)

Among recent contributions to this subject he cited Strauss, Cusani, Hirsch, Rae, Tourraine and Duperrat, Hajek and Dunphy. "In general, they present additional cases of spontaneous regression of malignant neoplasms in men, and emphasis that occasionally a malignant tumor will spontaneously recede, suggesting that some method of bringing this about at will may some day be achieved, and that spontaneous

regression should be considered in judging new therapeutic procedures, particularly when the evidence is limited to single-case demonstrations."

Long Term Recrudescences in Cancer: Shimkin cited Willis as having recorded 30 such cases, and noted: "The proclivity of recrudescence after years of apparent cure is particularly well known in intraocular melanoma. Cases have been reported of removal of the eye 10 to 30 years before the return of the neoplasm was heralded by the appearance of distant metastases." Breast cancer cases 20 to 40 years later, also the following individual cases: testicular cancer metastasized 11 years after orchiectomy; osteogenic sarcoma, 13 years after mid-thigh amputation; renal carcinoma 10 years after nephrectomy; recurrence 12 years after partial gastrectomy for gastric carcinoma.

"In the evaluation of long term recurrences, the possibility of a new neoplastic focus must always be considered. Multiple unrelated neoplasms are found in at least 4 per cent of patients with cancer coming to necropsy. This incidence exceeds the incidence to be expected from chance alone and will undoubtedly increase as the age of the population rises and as the number of patients cured of one cancer increases. The possibility of new neoplasms in patients apparently cured of one cancer is particularly high in sites where multiple independent foci are well known, such as the bladder, oral cavity, and colon. Increased incidence of second independent cancer is also to be anticipated in patients with neoplasms affecting paired organs, such as the testes, kidney and breast. The incidence of cancer of the breast is six times higher among women who have been cured of cancer of one breast than in women without previous mammary cancer. (Shimkin, 1951)

Hauschka (1952), in a survey of immunologic aspects of cancer, reviewed the literature representative of factual as well as theoretical developments, largely from 1942-1952.

"The field of tumor immunity, when last surveyed, was characterized by a pre-occupation with induced resistance and diagnostic serology. During the ensuing decade, emphasis has shifted toward problems of tissue specificity and a more basic concern with the genetic control and chemical nature of cellular antigens. Improvements in centrifugal and enzymatic fractionation and purification procedures, isotopic labelling of gamma globulins, and synthesis of protein-carcinogen conjugates have opened up new possibilities for immunochemical investigations. Meanwhile, the biologic attack on the question of distinctive tumor constituents has profited from advances in immunogenetics and virology.

Experimental design in general appears to have been influenced by Woglom's sobering admonitions and is today guided by a more critical awareness of genetic and serologic pitfalls. Although the outlook toward clinical application of new facts is no less dim than it was 10 years ago, the advantageous use of sensitive immunologic techniques should contribute greatly to a fuller understanding of differences between tissues in biochemical terms. The question whether the malignant change involves a gain, loss, or qualitative alteration of antigenic components is relevant here and will demand further probing into almost every aspect of cell function and constitution.

"Transplantation immunity need no longer be viewed as 'some novel and mysterious process', but conforms in main outline with the immune state generated by infection. A spontaneous tumor is not a foreign tissue, hence cannot evoke as measurable a response as the iso-antibodies elicited by grafts. Neoplastic antigens proper may indeed be ephemeral; yet, the reality of auto-immunization in health and disease argues against. . . abandonment of the search for them.

"The ramified subject matter has been organized into five chapters: (I) The immunogenetics of tumor transplantation; (II) Induced Immunity and hypersusceptibility; (III) Neoplastic antigens and the question of their specificity; (IV) Im-

munologic approaches to therapy and protection against carcinogens; and (V) Cancer diagnosis by serologic methods. Some recent consideration of specific antigenic entities in malignant cells, iso-antibodies in tumor transplantation, growth-inhibitory and enhancing effects of nonliving tissue fractions, host and extraneous factors in heterologous grafting, and the concept of tumor autonomy should supplement the following discussion with viewpoints of sufficient variety for a balanced appraisal of current trends."

In the section on induced immunity and hypersusceptibility, Hauschka noted the work of Aptekman who produced tumor atrophy by strangulation. "It is interesting that tying off the blood supply for as little as 24 hours induced immunity, whereas the surgical excision of an untreated sarcoma or carcinoma after 8-13 days of growth did not bestow resistance. The degree of response to oncolytic prophylaxis could be selected for, so that the percentage of immunity (82%) inducible among the offspring of successfully treated mothers was greater than that (50%) in litters from non-selected parents.

Hauschka noted that the difference between resistance and hypersusceptibility was sometimes merely a matter of small versus large dosage of antigenic material. Gorer (1942) has confirmed the earlier results of Tyzzer showing that antibodies may sometimes stimulate growths. This is most likely to occur in the presence of a relative excess of antigen.

NEOPLASTIC ANTIGENS AND THE QUESTION OF THEIR SPECIFICITY:

Viral Antigenicity: "The antigenic nature of filtrable causative agents of avian sarcomas, the Shope rabbit fibroma and papilloma, and certain mouse mammary carcinomas has been the subject of intensive investigation, justifying the conclusion that the ability to elicit neutralizing and other more or less specific antibodies is indeed a characteristic of known tumor viruses. . . When sera of fowls were tested one or two years after recovery from Rous Sarcoma they still gave a high titre of neutralizing antibodies to the Rous agent. The demonstration of active antibodies in such birds may be regarded, by analogy with other virus diseases

as evidence for the continued presence of neoplastic virus, although no further tumors are being produced. Hens that are carriers of the Rous virus lay eggs containing a considerable amount of virus-neutralizing antibody in the yoke. Since virus was not detected in the eggs, embryos or chicks derived from these carriers, however, it was concluded that transmission via the egg is possible but is probably not an important cause of the high incidence of neoplasms in poultry."

The experiments of Duran Reynals and his associates on the age and species dependence of natural neutralizing antibodies against chick and duck variants of the Rous sarcoma agent, and on the immunological implications of virus mutability have not only revealed pronounced antigenic shifts coincident with the processes of adaptive change, but have strengthened the doctrine of an infectious cancer etiology by deriving several lines of histologically distinct neoplasms and leukoses from induced variations of a single virus. Resistance or susceptibility of host tissues which themselves undergo ontogenetic changes in antigenic specificity and their multiform responses to an agent of fluctuating antigenic potentials - ranging from epithelial growths and lymphosarcoma through multiple bone tumors to the induction of non-malignant new bone - assumes the proportions of a basic problem; immunodifferentiation in histogenesis not only in the case of chicken sarcoma, but also in rabbit fibroma. The neoplastic effects of a virus depend on immunological factors for degree and type of expression.

Several tumor viruses, notably the rabbit papilloma agent (Shope), are intermittently "masked", hence detectable only by serologic search for the specific antiviral antibody.

". . .the partnership between such a cancer (V 2 carcinoma) and the virus endured for five years of transplantation in domestic rabbits; all later tests for the specific antibody in the blood were, however, negative. Had the virus merely ridden along as a passenger until it was lost? Apparently it was no longer essential for the continuing malignancy of the V 2 carcinoma cells."

The Bittner milk agent, functioning synergistically with genetic constitution

and hormones in the production of mouse mammary tumors, is highly antigenic under certain experimental conditions. Complement-fixing antibodies and precipitins for the mammary tumor agent have been reported. In rabbits or rats it elicits inactivating antibody effective both in vitro and in vivo. If, as is probable, the milk factor is a virus, it should behave as an antigen not only toward foreign hosts, but also toward the susceptible species; in mice, however, neutralizing immune bodies could not be clearly demonstrated."

The obstacles hampering unequivocal antigenic typing of neoplastic viruses have their counterparts in other branches of virology. Some pathogenic viruses do not give complement fixation in mixtures with their specific antisera or cannot be extracted from tissues diseased by them either in sufficient amount or in suitable form for in vitro serological demonstration. . . One therefore, should not expect that, even if specific antigenic tumor components are viruses, they may be entirely disassociated from normal protoplasmic constituents.

"During the events which lead from precancerous metaplasia to malignancy, or during the course of subsequent transplantation, cells may acquire constituents not found in their benign prototypes.

"The most exhaustive studies of an antigenically distinctive substance, regularly associated with a mammalian tumor, are those of Kidd, Friedwald and MacKensie in the Brown-Pearce rabbit carcinoma (1941 to 1952). . .

"The non-infectiousness of extracts containing Brown-Pearce antigen in high titre and the inability of host cells to protect the tumor substance against attack by its specific antibody (whereas neoplastic cells normally provide such amnesty for viruses) argue against the virus nature of the distinctive constituent. Kidd (1946) prefers to view it as an autocatalytic cytoplasmic determinant of proliferative activity. This interpretation hinges largely, but somewhat inconsequentially, on the apparent antiblastic effect of the corresponding antibody exerted against Brown-Pearce cells during incubation in vitro and also potent in vivo. Rabbits previously injected with cell free extracts containing the serologically active material resisted tumor grafts if their sera contained the specific antibody.

If. . .they had failed to develop the antibody, they were regularly susceptible. Experimentally induced immunity had nothing in common with the unknown factors causing spontaneous regression. The latter occurred more often in the absence of the specific antibody than in its presence, while sera of rabbits which had spontaneously recovered from the tumor did not inhibit the malignant cells in vitro unless they contained the antibody.

One significant factor which Hauschka noted was that antibody titres were enhanced by the synergistic influence of staphylococcus toxin administered simultaneously with the tissue antigens, a technique which should be more widely employed in boosting measurable responses to weakly reactive constituents of malignant cells.

Hauschka noted that there is a general decline in antibody production found associated not only with well established malignancy, (Parfentjef et al. 1951) but occurring soon after the application of certain hydrocarbons. (Hoch-Ligeti, 1941; Malmgren and Bennison, 1952). . .

"The evidence for quantitative, if not qualitative differences in the antigenic components of normal and neoplastic tissues is. . .convincing." Not only are the immune bodies described (complement fixing, and neutralizing antibodies, precipitins, lipins, agglutinins, and antiblastins) of the same types as those familiar to microbiologists, but the similarity between tumor immunity and resistance against parasites is further emphasized by the protective functions which cellular elements of the reticulo-endothelial and lymphatic systems perform in both neoplasia and infectious disease. (Murphy, 1926, 1941; Rodrigues, 1940; Stern, 1941) The lymphocytic theory of antibody formation, as revised by Ehrlich and Harris (1945) is in keeping with observations on the coincidence of tumor decline and lymphocytic activity, as well as the finding that there is a reversible exchange of antibody between normal and malignant lymphocytes, and that the latter may even exceed the former in their demonstrated capacity for antibody production (Dougherty, et al. 1945).

IV. IMMUNOLOGIC APPROACHES TO THERAPY AND PROTECTION AGAINST CARCINOGENS

Although effective "immunization" against transplantable tumors does not inter-

fere with the strain-characteristic incidence of spontaneous neoplasia of the same histologic variety as the immunizing graft, and although passive transfer of experimental immunity by means of cell-free sera or therapeutic trials with antisera "specific" to various tumors and antisera homologous normal tissues, have generally met with failures, a hopeful attitude relative to serologic therapy persists to this day in some quarters.

The apparent role of the reticulo-endothelial elements in defensive phenomena around and within foci of cancer tissues was the guiding impetus in the work of Bogomolets (1943) and his school with anti-reticular cytotoxic serum, small doses of which may stimulate the cellular protective reactions. A C S was prepared by inoculating horses with spleen and bone marrow from healthy persons who had met sudden accidental death. Its use is said to have brought about the disappearance of metastases and to have considerably diminished recurrences after operations for gastric and lung cancer. Tests with A C S in other laboratories showed inhibition or enhanced malignancy (depending on dosage) of the Brown-Pearce rabbit carcinoma (Movitz, et al. 1949) and a reduced incidence of spontaneous mouse mammary adenocarcinoma (Heiman and Meisel, 1949) but failed to affect the growth of Carcinoma 2426 and Fibroma 2011 in rats, or Sarcoma 180 and mammary tumors in mice (Heiman and Meisel, 1949). Reticulo-endothelial immune serum (R E I S), a preparation basically similar to A C S, inhibited Walker rat sarcoma 319 in vitro, provided homologous rat spleen had served as antigen (Pomerat, 1945). Sarcoma cells were not harmed by intimate contact with splenic fragments growing in the same flasks; but in these two-membered cultures REIS injured sarcoma at concentrations lower than those needed for damaging effects in the absence of spleen.

Treatment with bacterial toxins (Nauts, 1947, 1953) and with Shear's *Serratia marcescens* polysaccharides (1943) has several important immunologic implications and complications. The polysaccharide branch of chemotherapy is traceable to observations of local tissue reactivity, i.e., the Shwartzman phenomenon, in a transplantable liposarcoma of the guinea pig experimentally sensitized with bacterial filtrate. The tumor responded to intravenous challenge by tumor hemorrhage and ne-

crosis (as have many mouse tumors and some human neoplasms since then), while normal host tissues remained relatively unaffected. Since the bacterial toxins elicited equally extensive hemorrhagic disintegration in the non-sensitized control tumors, prior accidental sensitivation by a cross-reacting microorganism or virus was postulated. (Gratia and Linz, 1931)

A large investment of cooperative effort. . .has gone into screening a range of antigenically distinct polysaccharides and into attempts to detoxify them, and separate their potent antigenicity from their oncolytic property by chemical modification (Creech, 1949). It is now possible to protect mice passively by anti-polysaccharide sera against the usual toxic syndrome without decline in the tumor-destroying capacity of the antigen (Creech, 1948).

Both *Serratia marcescens* culture filtrate and Shear's polysaccharide are capable of eliciting the phenomenon of local skin reactivity. Shwartzman (1944) found no measurable alteration in antigenic specificity (immunizing value, precipitation and neutralization reaction) consequent to tryptic digestion and other purifying methods employed by Shear. Hence, the principles producing the Shwartzman phenomenon are akin to or identical with the factors inducing hemorrhage and regression in certain mouse tumors.

The hemorrhagic response of experimental tumors is, however, by no means specific to bacterial products, since it has also been invoked through histamine or through anaphylaxis in mice sensitized to normal filtered horse serum.

The demonstration of antibodies against body secretions, organs, components of normal tissues and distinctive constituents of some tumors (Kidd, 1946), has suggested the potential usefulness of immune bodies for selective localization of metals (McClintock and Friedman, 1945), dyes, and radioactive tracers in malignant lesions.

Under the synergistic influence of adjuvants, such as staphylococcus toxin, - titres against weak tissue antigens have been stepped up in the donors of anti-serum (Maculla, 1947) and after differential absorption a specific globulin fraction could conceivably be isolated and isotopically labelled.

First steps in this field have been taken by Pressman and his associates (1949) who have obtained zones of localization of radio-iodinated antibody in mouse and rat kidney. . .

Landsteiner's classical experiments achieved antigenic specificity of otherwise inactive molecules of known structure by their conjugation with proteins. The problem of an immunological defense against carcinogenic processes through haptenic activity of carcinogen-protein conjugates offers challenging possibilities for immunochemical synthesis and co-ordinated prophylactic experimentation. Creech and others (1947-1949) have coupled various serum albumins with isocyanates of a representative range of polynuclear aromatic hydrocarbons. Injection of the conjugate into rabbits elicited antibody which was precipitable by conjugates of the homologous hydrocarbon with a heterologous protein. These serological reactions were entirely dependent on prosthetic group activity, hence strengthened the feasibility of protection against carcinogenesis by chemo-antigens. . . More critical recent tests with C57BL mice (inbred for low spontaneous tumor incidence but very responsive to treatment with carcinogenic compounds) should evaluate the hypothetical protective efficacy of conjugates recently synthesized from proteins and certain systemic carcinogens. (Creech, 1952)

V. CANCER DIAGNOSIS BY SEROLOGIC METHODS

Cancer appears to differ biochemically from normal tissues in a quantitative rather than the qualitative sense, which bespeaks synthesis not of specifically abnormal substances, but of normal molecules at the wrong time and in the wrong places and amounts (Toennies, 1947). . . So far the search for minute increments of cryptic tumor proteins and other unknown metabolites amidst the massive output of normal cells during early stages of metaplasia had defied electrophoretic, ultra-centrifugal and solubility methods. (Hughes, 1951) Even during advanced stages of the disease, electrophoretic studies of plasma proteins and nitrogen, and lipid analysis of plasma fractions have revealed no characteristic deviations from the pattern of other ailments (except in multiple myeloma). Generally, the albumin concentra-

tion decreases and the alpha-globulins and fibrinogen increase while the shift in beta and gamma-globulins is not appreciable before the onset of cachexia.

Thus diagnoses based on immunologic principles rather than on much less sensitive chemical methods has continued to challenge experimentation. The optimism behind these attempts is founded on the immunologic specificity of certain normal tissues, on demonstrations of more or less "specific" antibodies evoked by transplantable tumors, on the antigenicity of some neoplastic viruses, and of carcinogen-protein conjugates, and on the existence in human serum of natural auto-antibodies formed against antigenic lipids which are liberated in tissue wear and tear.

. . .As yet there is great paucity of data on the antigenicity of malignant growths in man.

. . .Certain abnormalities of serum albumin often associated with tumor growth, such as decreased coagulability, solubility, and combining power for fatty acids, seem to depend on the presence in cancer sera of characteristic abnormal lipids which unite with the albumin (Hanke and Kahn, 1952).

Kahn's observations of immunity to lipids or lipo-proteins should stimulate further study of lipid serologic reactivity in the various forms of neoplasia. . . (Hauschka, 1952. He gives 220 references mostly 1941-1952)

Mefferd and Loefer (1953) noted that "Once neoplasia has commenced, the surrounding tissue responds with ill-defined resistance patterns and the neoplastic tissue may be overwhelmed, contained or practically unaffected. Only in the latter case will a gross inspection reveal a palpable tumor. It must be obvious that numerous loci of neoplasia, because of their very smallness, or because they already have been overwhelmed, are never recognized. . . It is likewise impossible to determine the exact time of origin or initiation of growth of such tumors."

Tumor Implantation: It is conditioned by the resistance level of the host strain and of individuals within the strain, and by the non-antigenicity (non-foreignness) of the tumor to the host. (Homologous tumors produce little or no detectable immunological response - for to all intents they are not foreign to the host's tissues.)

During the growth of a tumor, cells of lower vitality, viability, growth rate or potentialities soon are in the minority; thus one finds an increase in malignancy and autonomy with recurrent or metastatic tumors.

The success of tumor implantation depends upon what rapidly mobilizable defensive focus the host can elicit, and upon factors immediately affecting them, such as lymphopenia and lowered antibody response following a pyridoxine deficiency (Stoerck, 1948). Exposure to ionizing radiation causes a marked leukopenia, inhibits the production of antibodies (Hektoen, 1915), lowers the resistance to infectious diseases, and enhances the takes of homologous skin grafts and tumors (Toolan, 1951). Probably the mustard gases would likewise enhance transplantations, since they exert similar effects to x-rays (leukopenia, lowered antibody production). Since tumor cells are actually largely of non-foreign composition, unless transplanted to a foreign strain, it is not surprising that so little success had attended efforts to demonstrate acquired immunity.

The second response, coming in about a week, involves the elaboration of antibodies, to neutralize any foreign antigens which might be present, and the infiltration of monocytes and lymphocytes. These encircle the implant and tend to contain or destroy it. . . it is quite possible for these cells to destroy or neutralize

a certain rather definite number of cells in any implant, regardless of its size. The size of the implant therefore, becomes critically important. . .the larger the number present, the better the tumor can fare in the "soil" of the host.

Apparent lag periods or latency following induction or implantation may be explained as due to the interval required for the unneutralized neoplastic cells to gain momentum (number of cells x rate of growth) sufficient to overcome the defensive forces of the host.

Nutrition and Tumor Resistance: Forces other than the above are also operative in the expression of total resistance: it can be altered significantly by non-specific treatment of the host prior to tumor implantation. Sabine and Olitsky have demonstrated that during host maturation, barriers quite unrelated to humoral immunity develop, which block in adult animals the routes of dissemination of infectious disease which are possible in young animals. Sabine (1941) demonstrated that nutritional deficiencies prevented or retarded the appearance of some of these natural barriers.

Of very great significance was the discovery that caloric restriction lowers the growth of spontaneous tumors reported by Rous, (1914) Tannenbaum (1947) demonstrated this clearly in leukemia and in eight spontaneous or induced tumors. That the resistance mechanisms to implantation were strongly influenced by nutritional factors was demonstrated by supplementation of the diet with pyridoxine (Loefer, 1951) and thymic extract (Loefer and Geller, 1951). This treatment significantly enhanced implantation while a converse effect was noted following treatment with supplementary phenylalanine (Loefer & Mefferd, 1952). Mefferd noted that these effects are probably not the result of direct action on the tumor cells.

Resistance is thus a relative factor depending on many variables, such as size of inoculum, age of host and donor animals, and significantly, the nutritional state of the animal. As Clark et al (1949) pointed out, the evidence is clear that the typical clinical picture of several virus diseases can be markedly altered by a variety of dietary deficiencies. That hormones per se exert specific effects has

been established by Huggins (1941). Mefferd and Loefer "suggested that tumor growth is regulated as a result of a shifting ratio between nutrition (including related factors) and resistance.

These workers have correlated peculiar metabolic patterns, particularly those involving vitamin deficiencies, with certain diseases, and have shown further that these diseases (genetotrophic) may be successfully treated by suitable dietary supplementation; even though a physiological condition rests upon hereditary roots, a nutritional attack may be successful." It is now generally recognized that genes control enzymatic reactions. . . modification of the conditions surrounding the enzyme molecules, even though the quantity and specificity of the enzymes are basically gene controlled, can result in a change in the phenotype expression.

Mefferd and Loefer suggested that a basic research program be established on rats to study the differences in metabolic patterns between resistant and susceptible animals (quantitative determination of 30 or more physiological characters) and thus possibly determine the prime factors related to susceptibility. (Mefferd & Loefer, 1953)

In a paper entitled "Cancer as a Chronic Disease" Morton and Morton (1953) stated: "Scattered through the literature a series of remarkable cases indicates how unpredictable cancer is as a disease. In any series of untreated cases there will be certain ones with much longer survival than the average. Some apparently show spontaneous disappearance either of the primary tumor or of secondary implants. Some seem to grow in cycles with times of rapid growth alternating with stationary periods or actual recessions. And there is the phenomenon of delayed recurrence where the tumor reappears years later in the scar of the previous operation or in its immediate neighborhood. Sometimes the metastatic cells seem to have remained dormant in the lymph nodes or in organs of the body without ever producing symptoms. Sometimes after such a resting period the tumor cells seem to regain their vigor and flare up anew with rapid spread throughout the body. The balance between the growth rate of the tumor and the resistance of the host has been of interest to us for several years in the clinic as well as in the laboratory.

We have summarized cases which indicate that cancer may behave as a chronic disease. These cases cover a variety of cancers, showing that chronicity is not confined to any particular type." Morton then gives 17 histories of cases personally observed and a table of 46 cases reported by other physicians.

In the discussion Dr. Joe E. Meigs stated: "I think this is a very important paper. I would like to know whether Dr. Morton is carrying out any immunity studies and whether or not he is trying to find out whether he can boost the resistance of these patients. It is probably that many people have an immunity to disease which may be lost at certain times during their lives. I am sure we all have seen patients with cancer who have gone on for ten or twelve or more years after operation, and then suddenly the cancer may appear in various regions all at once - just as though something that protects them from recurrence is lost. I wanted to ask whether any work is being done in an effort to find out whether there is any immunity against cancer."

Dr. J.M. Finney, Jr., Baltimore, Md., stated: "A propos of what Dr. Meigs just

said about immunity, we know that for a long time it was felt that active tuberculosis and cancer did not exist together. I think that has been pretty well disproved. There came to my attention some years ago, via a letter from Asheville, where a man had died of active tuberculosis and on whom autopsy had been performed, a request for the description of an operation which he had had done by my father at Johns Hopkins. I looked up the old history and found that, 17 years previously, he had been operated upon for an adenocarcinoma of the stomach. A large part of the stomach was removed (it was not a total gastrectomy, but a near total one), and there was a note in the operative record that there were several enlarged glands high up under the diaphragm in the gastric mesentery, about 1 cm. in diameter, which felt as though they were involved in the malignant growth. I sent this message back to the doctor at Asheville, and I received in return an autopsy report stating in substance 'that the stomach showed evidence of having had an extensive resection with no evidence whatsoever of malignancy at the present time; but high up under the diaphragm there are six nodes about 1 cm. in diameter, all of which are almost completely replaced by adenocarcinoma of gastric origin.' Seventeen years!"

In closing, Morton emphasized three points: "First, although cases of this type are rare, they do occur and should be remembered when one in offering a prognosis to a patient or a family about carcinoma. Second, as mentioned by Dr. Meigs, in many cases there will be a long period of complete absence of symptoms and then, when the tumor reappears, it spreads very rapidly and the patient succumbs. Third, in these patients we are not talking about people who have just lived and dragged on with carcinoma, but people who have gone on with a long survival of active and useful life." (Morton and Morton, 1953)

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While much has been written about the markedly beneficial effects of concurrent bacterial infections on cancer, the data on the role of acute inflammation has been largely ignored, possibly because much of it was reported in the 19th century.

Menkin (1950) defined inflammation as a complex vascular, lymphatic and local tissue reaction elicited in higher animals by the presence of microorganisms and non-viable irritants, a basic reaction to injury whereby the deleterious agent tends to be localized and ultimately destroyed, i.e., an immunological mechanism. It may be elicited by physiological stimuli such as sunlight, or chemical stimuli such as bile or various bacterial or protozoal toxins. All produce an inflammatory reaction varying in intensity from a barely perceptible hyperemia to a suppurative process with abundant pus formation.

Menkin isolated a polypeptide from inflammatory exudates which he called leukotaxine. Diffusible, thermostable, this substance has no relation to histamine, which increases capillary permeability and migration of leukocytes, first polymorphonuclears then macrophages. The only substance capable of counteracting its effects on capillary permeability is adrenal cortical extract. Adrenalectomy results in marked enhancement of spreading reaction in animals. It is entirely counteracted by intraperitoneal injection of adrenal cortical extract. Hyaluronidase, in contrast to leukotaxine, does not cause migration of leukocytes.

The role of inflammation in immunity: When various materials or bacteria are injected directly into an inflamed area, these substances are retained or fixed in situ more firmly than under normal circumstances. This fixation occurs extremely soon with certain irritants, as early as 30 minutes after injection of a powerful irritant.

Bacteria are also inhibited in their normal rush into the systemic circulation in the presence of acute inflammation (Opie, 1929). Foreign proteins are also held in an acutely inflamed area. Antibodies and interferon which are also proteins may presumably also be retained in areas of acute inflammation. This point is of importance in designing the most effective technique of administering bacterial toxin therapy to cancer patients. It suggests the need for initial injections into the tumor

and its periphery whenever this is possible, in order to localize the lymphoid and reticuloendothelial cells and interferon.

It is well to remember that material injected at the periphery of an area of acute inflammation fails to enter such a focus, due to mechanical obstruction.

By circumscribing the irritant rapidly, the acutely inflamed area allows a certain interval of time to elapse and thus prevents general infection. This allows time for the leukocytes to assemble to dispose of the irritant through the process of phagocytosis. Thus by local damage the vital organs are protected.

Bacterial Invasiveness: Bacteria introduced into normal tissues are likely to invade the tissue and enter the general circulation, but microorganisms vary in this capacity: staphylococci remain localized, streptococci tend to invade extensively. One reason staphylococci are such a necrotizing organisms as to cause prompt lymphatic blockade, is that they produce a soluble toxin which per se is capable of causing lymphatic blockade. This soluble toxin is inactivated by heating to 58°C.

Menkin pointed out that invasiveness and virulence are two separate factors. Virulence refers to the innate toxic property of injuring tissue; invasiveness refers to the ability of an organism to spread from its point of entry either to the tributary lymphatic nodes and vessels or to the systemic circulation. One can interfere with the invasiveness of a microorganism, and yet its virulence may remain intact. (Menkin, 1950, pp. 57-58.)

Foreign protein introduced into the skin of a rabbit appears immediately in the blood serum, remaining seven to nine days, disappearing shortly after precipitin appears. With repeated injections of antigen the quantity entering the blood diminishes and with advanced immunization none enters unless massive doses are used. (This is what occurs in cancer patients receiving intramuscular, subcutaneous or intradermal injections of Coley toxins or other bacterial toxins and explains why they gradually ceased to elicit febrile reactions unless such massive doses were used.)

Phagocytosis: Metchnikoff showed that two cells are primarily concerned with phagocytosis: macrophages and polymorphonuclear leukocytes. The important phagocytosis-promoting substances in normal and immune serum are the opsonins and the globulins

which form a film over the surface of the object to be phagocytized. However, these opsonizing antibodies are not always necessary for phagocytosis to operate. Phagocytosis of bacteria can take place if the cells operate upon relatively rough surfaces such as filter paper and fiberglass, but on smooth surfaces such as glass, paraffin or cellophane, no phagocytosis occurs unless opsonins are added. This is an important point, for it is possible that in inflammation with the network of fibrin the cells behave in the same way, and in the presence of such rough surfaces, can phagocytize without an intermediary. Ehrlich (1945, 1949) in studying the functional significance of various leukocytes in inflammation, concluded that the neutrophils, pseudo-eosinophils and macrophages are catabolists in splitting the antigen into soluble antigenic fractions. The mast cells prevent coagulation, the lymphocyte destroys toxic products of protein metabolism and the plasma cells synthesize antibodies.

The Systemic Repercussions of an Inflammatory Reaction: Leukocytosis accompanying inflammation is partly referable to the liberation by injured cells of a globulin which acts on the bone marrow via the circulating blood, inducing the growth of granulocytes and of megakaryocytes. The leukocytosis-promoting-factor (LPF) liberated by injured cells into the exudate is non-diffusible and thermolabile. Menkin (1950) suggested the clinical use of this substance as possibly reinforcing the known antibiotics, especially since the prognosis in many diseases depends to a large extent on the number of circulating leukocytes.

Celcus pointed out that every type of inflammation is characterized by four cardinal features: rubor, tumor, calore, dolore (redness, swelling, heat and pain). Menkin added a biochemical feature: proteolysis or breakdown of proteins.

Inflammation leads to the disappearance of the basement membrane. This membrane contains glycoproteins whose condition of polymerization is apparently responsible for its properties and plasticity. Alteration in polymerization may be caused by enzymatic activity (hyaluronidase and collagenase). This depolymerization may be significant in changes of permeability of the capillaries.

Menkin discussed the fever-inducing capacity of the insoluble, thermostable euglobulin fraction of exudates. Fever very frequently accompanies inflammatory states. He termed this substance pyrexin (Menkin, 1950, p. 110).

The dog is a more reliable animal than the rabbit in inducing a febrile response with intra-vascular injection of inflammatory exudates. Jansco has noted that the histamine liberated in acute inflammation is a physiological activator of the reticulo-endothelial system.

Repair: One of the most fascinating subjects in general pathology is repair, the healing of inflammatory lesions. How is this accomplished?

When damage is merely to the epithelial lining, normal regeneration occurs by simple mitosis. When a clean cut wound is made at operation, relatively aseptically, and when the edges are brought together by suture, healing occurs rapidly by primary union. There is hardly any fibrin or exudate. Fibroblasts move to the line of incision. A few polymorphonuclear leukocytes may appear due to the injury caused by the knife. Within a few days firm union occurs, and more and more fibroblasts and their collagenous bundles are deposited. The result is a scar or cicatrice which becomes bloodless and usually persists indefinitely.

Repair of a lesion may start during the course of the inflammatory reaction when repair occurs simultaneously with the end stage of inflammation. One encounters mononuclears or macrophages, eosinophils, lymphocytes or plasma cells and varying degrees of fibrosis - the histologic picture of "chronic inflammation".

When a wound is open or if it suppurates, healing is somewhat slower and proceeds thus: the gap is filled with fibroblasts and eventually their inter-cellular matrix (collagen). Fibroblasts grow in abundance once the irritant has become localized and disposed of by the various forces already discussed. Fibroblasts need blood, which explains the active proliferation of the capillary endothelium. New capillaries sprout, from the base of the wound upwards. Vascular organization is the combination of reparative factors consisting of fibroblasts, capillary sprouts and numerous new lymphatic channels. Granulation tissue is as a rule very resistant to superimposed infections. After a long period more collagen is deposited. There is a tendency to

contraction, resulting in a cicatrix. For some reason not well understood, perhaps due to contraction of the dense deposits of collagen, devascularization occurs - "avascular organization".

Menkin's observations suggest that there is a growth-promoting factor or factors liberated by injured cells which may account for the proliferative forces in the region of injury.

In general, when the area of injury is severe an acute inflammatory process is likely to result, whereas when injury is mild proliferative reaction may ensue (Menkin, 1950).

Burrows (1932), in his monograph on the localization of disease, states: "At first sight the passage of colloidal and other particles through the vascular endothelium might be regarded merely as an attribute of inflammation, when the subject is examined with more exactitude, it becomes manifest that such permeation may occur in conditions other than inflammatory. Thus it is a pronounced and widely spread phenomenon of general shock and of the antibody-antigen reaction; it is a normal occurrence in the healthy placenta and the liver, in clean granulating wounds, in the brain following concussion, and in certain special forms of poisoning. The endothelium of the capillaries in and about a scar may remain more permeable than normal for long periods of time in the absence of any ordinary evidence of inflammation." Also some *maevi* and...dusky areas of a mottled skin react in the same way.

Diapiresis: The passage of colloidal or other particles of suspended matter, including bacteria and blood cells through the unbroken walls of the blood vessels, is diapiresis. The normal fate of foreign colloids and suspended particles depends on the electrical charge they carry; most substances (blood cells, bacteria, proteins and other colloids) are negatively charged when carried in the blood. In the absence of any local inflammatory or other condition involving diapiresis, electronegative foreign substances are speedily removed by the phagocytic cells which line the sinusoidal blood spaces of various internal organs: liver, bone marrow, and spleen especially. Inflammation, when present, modifies this, so that the capillary vessels of the affected tissue appear to become phagocytic, and certainly become traversed with foreign particles.

Degrees and results of inflammation vary greatly according to the intensity and duration of the irritation. They also differ in kind. One irritant produces a local concentration of polymorphs, another an exudate containing mostly mononuclear lymphocytes and macrophages. Such differences may be of considerable therapeutic import.

The injured cell, although surviving the injury, may not invariably make a perfect recovery, but may continue to be too permeable.

The size of particles influences the speed with which they traverse the endothelial cytoplasm. (Pigments and viruses much faster than bacteria.)

Localization of Foreign Proteins: Not only do foreign proteins gain entrance to the extravascular regions, but under the influence of inflammation they remain there. In other words, if a foreign protein be introduced into the blood stream, it will become concentrated in any focus of inflammation that is present - retained and concentrated.

Localization of Dyes: Colloidal dyes, carrying a negative electrical charge, when injected into the blood stream are taken up by the sinusoidal endothelium of the reticulo-endothelial organs, especially in the liver, bone marrow, and spleen. When a focus of inflammation is present, an alternative destination is provided. This localization of colloidal and other matters in the reticulo-endothelial organs and in inflamed tissues seems to be but little influenced by the chemical constitution and special affinities of the matters themselves, and to depend entirely on the nature of the electrical charge which they carry, and on the size of the particles. Only negatively charged particles become localized by inflammation.

Schmidt found that after exposure to x-rays the connective tissue cells took up increased amounts of trypan blue. Echstein and Von Mollendorff noticed increased coloring of skin with trypan blue after ultra-violet radiation.

Roosen reported that localization occurred after intravenous administration of isamine blue in tuberculous glands and other pathological tissue. Anitschkov stated that any active hyperaemia would increase the passage of dyes through the vascular endothelium. In fact the distribution of colloid substances after their intravenous introduction could be quantitatively changed by thermal or other stimuli.

Okuneef (1924) applied a hot water bottle to the abdomen of a rabbit, and then gave an intravenous injection of trypan blue: the belly wall (where it had been in contact with the bag) and the subjacent coils of intestines were strongly colored. Okuneef (1924) confirmed Goldman's observation that a functioning mamma collects trypan blue.

Roosen has observed and has made use of the fact that isamine blue becomes localized in tissues subjected to diathermy.

Aseptic inflammation was set up in subcutaneous tissues. The irritants used were agar, gum, kaolin suspended in 5% gum solution, and Coley toxins.

Diathermy applied to a rat's thigh also caused a pronounced deposit of trypan blue in the superficial and deep structures which lay between the electrodes. Concentration of localization differs considerably between individual animals.

Electropositive dyes are much more toxic than electronegative dyes and they are rapidly absorbed by the oppositely charged proteins of the blood and blood vessels; the latter are mainly deposited in the reticulo-endothelium of the liver, bone-marrow, spleen and lymph nodes, and also, when the presence of inflammation permits of their exit from the blood stream, in the macrophages of inflamed tissue, but they have little or no tendency to enter the parenchymatous cells, for example the secretory cells of the liver and pancreas.

"One curious and perhaps significant fact is reported by Von Jansco, namely that colloidal metals are not taken up by the reticulo-endothelial system if, just previous to their injection, one of the anti-coagulants -- heparin, nove-rudin or germanin -- is administered." Hirudin he found without influence in this respect.

Unexplained selective affinities exist between particular tissues on one hand and various substances, including alkaloids, toxins, pigments, viruses and bacteria on the other.

Localization of Syphilis: The special tendency of the earlier general manifestations of syphilis to appear in areas of irritation is now an accepted clinical fact (including in tattoo marks).

Localization of Bacteria: "The evidence available to prove that bacteria are sometimes collected from the blood stream by inflamed and otherwise altered tissues is conclusive. Clinical instances are numerous and striking. The phrase 'locus minoris resistentiae' is hoary with years, and the initiation of local infective processes by injury unaccompanied by direct infection is a widely recognized fact."

Burrows cites tuberculosis experimentally produced in animals: lupus in sun-burned or chilblained tissues, not those protected by clothes.

Kettle found that if a local subcutaneous inflammation were produced by introducing calcium chloride or turpentine, and the animals were subcutaneously inoculated

intravenously with tubercle bacilli, these became localized in the inflamed tissues. He further obtained a similar fixation of the tubercle bacillus in subcutaneous lesions effected by silica. But whereas the inflammation set up by calcium chloride or turpentine was more severe than that caused by silica, the fixation and proliferation of the tubercle bacillus was much greater in the lesions caused by the silica. Burrows noted that "this is in accordance with the clinical and experimental information collected in this volume; that is to say, the gentler irritants may be more effective agents in causing localization. In other words, localization does not bear a direct proportion to the degree of irritation."

That living organisms after lying dormant for long periods of time in the tissues may be awakened into sudden pathogenic activity is recognized. The recrudescence of inflammation in tuberculous joints as a sequel to injudicious movements, or the flaring up of sepsis in old wounds after surgical interference, are notable examples.

Leprosy: Leprosy follows the same rules of localization in the skin as does tuberculosis.

Bacillus Typhosus: There are very numerous examples of typhoid abscesses developing at sites of hypodermic injections of various substances during a case of typhoid, thus localizing the bacilli in the inflamed area.

Benians (1921) experimented on this subject. He injected various substances (gum tragacanth, mucin, starch, agar, McConkey's bile, salt agar and muscle extract) into the subcutaneous tissues of rabbits and then injected bacteria into the ear vein. He found that *Escherichia coli* (non-motile form), *Bacillus typhosus* and *Bacillus paratyphosus* readily became localized in the areas injected with the above substances and were isolated therefrom. *Staphylococcus aureus* usually could not be recovered, and *Micrococcus catarrhalis* and streptococci were never recovered at all. Egg albumin and mutton fat failed entirely to localize bacteria from the blood stream.

Pneumococcus: Like typhoid bacillus, pneumococcus readily becomes taken up by inflamed tissues, in which it may cause suppuration. Zuber, in his thesis on the localizations accidentally produced during the course of pneumonia, described a case in

which abscesses containing pneumococci occurred at the sites of hypodermic injections of caffein benzoate, and he collected a great many similar cases in the literature.

Streptococci: Rolly (1923) recorded a case of severe puerperal sepsis in which the patient received 24 subcutaneous injections of a silver preparation in the lower limb. Abscesses developed at these punctures and the patient recovered. Burrows cited other similar cases in which streptococci were concentrated or localized in sites previously inflamed by silver nitrate or other substances.

Fixation Abscess: "Hippocrates observed the favorable effect which local abscesses seemed to have upon the prognosis in certain diseases, and recognized the value in treatment of hot fomentations and counter irritation.

"Jenner was a firm believer in the efficacy of artificial inflammation in diverting disease from vital parts. 'May we not,' he asked, 'by making new diseases, check the progress of disease in a vital organ or in a part where it may be unmanageable, by substituting another which is under control? Whoever has observed the deranged state of health where vesicated disorders have been called into action by an effort of nature, must have seen how often they arrest the progress of the original disorder, and may we not from thence infer what appears to be a pretty general law of nature, that she often gets rid of diseased action affecting vital organs, by exciting eruptions in other parts not vital. I am aware that this doctrine is not entirely new; but though the phenomena have been so often described, have we taken the hint in our treatment of diseases, either chronic or acute?'

"Jenner gives references to earlier literature on the subject, and described his own method of treatment, which consists of gentle and repeated rubbing of a stimulating ointment into the skin of the inner sides of the arms or other convenient area, until an eruption resembling herpes had been produced in the treated parts. The prescription ...Antim. tartrat. (subtil. pulv.), 2 ounces; Ung. cetacei, 9 ozs.; Sacchari alb., 1 oz.; Hydr. Sulph. rub. gr.V; M. Ft. ung.) An increased proportion of tartrate will, he says, cause earlier inflammatory results.

"In spite of the fact that belief in the efficacy of counter-irritation as a

remedial agent has endured so long in tradition and has been so firmly upheld by leading minds in the profession, the principle involved appears never to have played a dominant part in therapy - possibly because its mechanism was never freely understood. A great deal of new interest was attracted to the subject when Fochier (1892) published his paper on the treatment of puerperal infection by subcutaneous phlegmon. The fundamental observation which had led him to adopt this method was the sudden amelioration which sometimes came about in a general infection coincidentally with the formation of a localized abscess." Fochier still has many followers in France, particularly in his own district, Lyons, but relatively few elsewhere. Good results have been claimed for the method in a variety of ailments: puerperal fever (Fochier, Gonnet, Madrids); various kinds of septicaemia and severe sepsis (Snapper, Jacob, Villaret et al, Boidin, Lesné et al, Espenal); pneumonia (Conor, de Lostalet, Destefano et al, Todd, Guérat); encephalitis (Netter, Martin); Malta fever (Roziès); malaria (Carlès); a virus septicaemia following rat bite (Brodin and de la Rivière); and various other diseases including severe Jacksonian epilepsy (Ricaldoni); poisoning by toad stools (Pic and Martin) and by mercuric chloride (Aquino).

"Some of this therapy may at first seem bizarre, but not if considered in the light of such clinical and experimental knowledge as can be derived from a study of deliberate fixation abscesses, and also of those accidental fixation abscesses which have followed hypodermic injections and local lesions due to other causes.

"Fochier injected rabbits with anthrax, and into some of these he injected subcutaneously in a different spot 0.25 cc. of turpentine. All of the controls died in the usual time, about 66 hours. However, some of the rabbits treated with turpentine survived, while others, although dying, outlived the control animals.

Findlay made a study of the hematogenous infection in rabbits. Bacteria were injected intravenously, and immediately afterward flank injections of histamine were made on the right side and a phosphate buffer solution of the same pH(7.2) on the left. Only in the histamine areas were the bacteria localized: *Staphylococcus aureus* (three strains), *Streptococcus hemolyticus* (one out of two) and a pneumococcus.

Inflamed tissues not only segregate bacteria from the blood, but retain them and prevent their direct spread to the neighboring parts.

It is probable that when Coley toxins or other bacterial products are given intramuscularly remote from the tumor such inflamed injection sites may localize the toxins given at subsequent injections and keep them from reaching the tumor cells.

Localization of Viruses: Burrows stated: "Just as no doubt can be held concerning the localization of bacteria from the blood stream by inflamed tissues, so none can be entertained as to the localization of viruses."

Measles: Hebra noticed that if a patient during the prodromal stage of measles had been lying for some time on one side, the rash was apt to become apparent first in the arm upon which his weight had been resting, and he further observed that if ointments, plasters or lotions are applied to the chest, the rash would often first show itself in that region. The rash was also, he noted, very prone to appear in any part which was compressed by tight bandages or articles of clothing.

Schick noted that to older doctors it was well known that bandaging or the application of iodine could lead to a copious outbreak of spots if these applications were made during the prodromal stage of small pox.

Von Pirquet, in a classic paper, discussed the distribution of the rash in measles with great care, and concluded that the spots appear in all chronically hyperemic areas earlier than in the normal skin, no matter what the cause of the hyperemia. Anemic scars remain poorer in rash than the surrounding skin, though the tissue immediately adjacent may show a particularly rich crop of spots.

Experimentally Von Pirquet found he could influence the distribution of measles rash by a variety of cutaneous irritations provided that they were made in the prodromal period, at least one day before the general eruption came out. Thus a mustard plaster applied to the patient's leg during this stage led to the outbreak of a confluent eruption over the entire area so stimulated. Mere bandaging of a limb was followed by an early appearance and an increased profusion of spots. Venous congestion caused a delay in the appearance of the maculae, followed by a rich crop.

(Comment: These observations suggest that in order to assure that bacterial toxins be absorbed throughout the tumor area, an electric pad, hot water bottle or a mustard plaster might be applied ^{locally} 10-30 minutes prior to the toxin injection given in or near the tumor.)

Smallpox and Vaccinia: Hebra stated that when a person previously affected with any other acute or chronic skin disease -- eczema, psoriasis, syphilis, etc. -- was attacked by small pox, the exanthem developed with peculiar intensity on the parts that were already unhealthy.

Tieche also noted that in variola the rash appears copiously where any irritation of the skin is present, and that in these areas vesicles are often confluent, so as to give the appearance of a burn. Ordinarily the rash is least abundant in the regions of the body most protected from irritation, i.e., the loins and abdomen.

Jenner remarks that if children suffering skin lesions were vaccinated in the arm, typical vesicles not infrequently appeared on the affected parts of the skin. "I have seen many instances where pre-existing pimples have been converted into vaccine pocks which have kept pace with those on the arms in their progressive changes."

Denney and Hopkins vaccinated 118 lepers and 105 non-leprous attendants with the same lymph and found that among the lepers not only was the local vaccinal response severe and often accompanied by necrosis and ulceration, but there was general fever and acute temporary exacerbation of all leprous lesions. No abnormal effects occurred in the leprous-free attendants. Burrows believed that the vaccinia virus may become localized by the chronically inflamed leprous lesions, a widely-distributed, though modified vaccinal eruption being thus brought about.

Calmette and Guérin's work gave laboratory confirmation of the fact that vaccinia virus may be localized in irritated tissue (rabbits), provided that the irritation was induced within 24 hours after the injection of vaccinia. If an interval of 48 hours elapsed between the injection of the virus and the epilation, no localization occurred in the denuded area.

Camus has also noted the tendency of vaccinal virus, when given intravenously to rabbits, to become localized in recent scars, on naevi, on shaved skin, about small

burns, in areas of skin to which chloroform had been applied and also in areas affected with chronic eczema. To get consistent results large doses of virus must be given. He noted that scratching of the skin added nothing to the influence of the razor. Vesicles were often absent from the scratch marks, and in any case did not show a special tendency to appear along these lines.

Levaditi and Nicolau verified the fact that after intravenous injections of vaccinia virus in rabbits the subsequent cutaneous eruption occurred particularly in areas where the skin had been irritated. Vaccinial lesions of the eye were produced in a similar way by scarification of the cornea or by exposure to x-rays prior to intravenous administration of the virus.

Duran-Reynals effected localization of intravenous injections of vaccinia virus in 25 out of 29 places where either chicken embryo cultures or chicken sarcoma cultures had been previously injected. Peptone and Kieselguhr failed as localizers.

Hoffman and Duran-Reynals (1931) observed that if an extract of testicle was given intracutaneously and vaccinia virus intravenously the subsequent virus infection was sharply localized to the part of the skin in which testicular extract had been injected. Thus many investigators have proved that vaccinia virus becomes localized in inflamed skin.

Ultra-violet radiation inhibits vaccinia eruption whether given before or after inoculation. X-ray radiation prior to inoculation also inhibits the eruption in irradiated areas. The heavier the irradiation the greater the inhibition.

Varicella: Swoboda refers to the localization of the rash by bandages and tight clothing.

Rivers and Tillett (1925) give details of cases illustrating the influence of irritation on localizing the rash: adhesive plaster had been applied to ankle; diaper rash was present; a tight necktie with a soft collar had been worn; acne on the face. All four developed more varicella vesicles in the irritated regions. In a later paper these authors reported a patient with secondary syphilides who developed chicken pox and the spots were localized in the skin areas affected with syphilis, face, scalp,

extremities.

Scarlet Fever: This rash follows the same general rule of localization for the rashes of fevers due to viruses. Hebra long ago noted that the rash appeared first on regions which had been kept warm, or had been previously exposed to pressure or friction.

Heim and John published a case under the title, "The re~~infl~~ammation of a cutaneous reaction that had already passed away, during an attack of scarlet fever." A child of four was given three doses of different tuberculines into the flexor surface of the left forearm. These excited no general or local reaction. On April 13 the child developed scarlet fever (104⁰F.), a sore throat, and a typical rash on face, neck and chest, none on abdomen or extremities. To their great astonishment, Heim and John found a re-inflammation of the three inoculation sites of a month previously. Two days later the rash spread over the entire body, and the "revived papules were surfeited with it." At this time the later tuberculin injections made between March 23 and April 10 first showed pronounced local reactions with reddening and infiltration.

Martland proved that the localization of the lesions of hoof and mouth disease in guinea pigs is due to pressure and slight traumatism. By bandaging the foot of an animal suffering from this disease in cotton wool he prevented lesions developing on that foot, although its unprotected fellows all developed typical lesions. Burrows felt that it was remarkable that such relatively slight and normal stimuli as the pressure on the feet when standing, and the small injuries received by tissues of the mouth during eating were sufficient. Such minor traumata apparently are insufficient to bring about the localization of most bacterial infections. It is possible that the discrepancy may be due to the smaller size of the virus as compared with bacteria, because the ease with which diapedesis is effected appears to depend to some extent on the effective size of the particles. (Comment: The smaller the particle the less the degree of permeability required for its localization. Therefore viruses may be localized by lesser stimuli than those needed for bacteria. This point should be considered in the preparation of toxins for treatment of cancer patients. They may require a spreading factor to increase the permeability of the tissues. Perhaps that is why

streptococcal infections have produced the majority of so called spontaneous regressions in cancer patients. Streptococci produce hyaluronidase, a potent spreading factor.)

Hyperemia by itself has little effect in causing exudation, but when associated with increased capillary permeability it leads to a pronounced increase of exudation. Thus it not only assists and accelerates the localization of viruses from the blood stream but it facilitates the production of vesicles.

Tumor-Producing Viruses: Epithelial injury is the one great factor in determining the localization of virus of epithelioma contagiosum, whether the virus is applied externally or circulates in the blood stream. Burrows cites Burnet, Goodpasture and Findlay's experiments.

Moses found that if some of the hair of an animal were plucked, an intravenous injection of infective myxoma in rabbits was regularly followed by extensive severe lesions in the depilated area.

Comparable effects were obtained with the Rous chicken sarcoma. Rous, et al, suggested that injury might be a factor in the infectivity of cell-free filtrates. They observed that such a filtrate of Rous sarcoma was more likely to produce a tumor if a little diatomaceous earth was added to it.

Other experiments were made by Pentimalli using red-hot cautery on various internal tissues after laparotomy. He also concluded that the virus of Rous sarcoma, and the cellular elements also, become selectively localized in tissues which have been damaged. Suzue came to a similar conclusion, having observed that injections of Kieselguhr, lycopodium or powdered charcoal into any part of a chicken suffering from sarcoma led to the formation of a metastases at the site where the foreign substance had been injected (muscles, liver or lung).

Mackensie and Sturm, in similar experiments injected various substances including embryonic tissue, Scharlach-R, Kieselguhr and tar and concluded that the earlier stages of the inflammatory reaction localized the tumor agent more regularly than the later stages.

Similar localizing effects of inflammation were recorded by Fujinami and Hatano, who stated that if simple granulation tissue or inflammatory spots are created in any

portion of a sarcoma-bearing chicken, the tumor-producing agent operates there and often results in the formation of a sarcoma.

Findlay produced local tumors after injecting histamine in the right pectoral muscle of fowls who had received an intravenous or intraperitoneal dose of a cell-free filtrate of Rous sarcoma.

Localization of Cancer: The development of a spontaneous neoplasm may be due to a local concentration under the influence of chronic inflammation of some cancer-producing or cancer-favoring substance present in the blood. It may be also that often repeated or continued stimulation of cells prepares them in some manner for an indefinite period of multiplication with imperfect differentiation. It may be that apart from its power of localizing the cancer-producing substance, irritation in itself is inimical to cancerous growth.

When an epithelioma develops in connection with an old scar, the growth appears often in the margin of the scar, which is precisely where the localization of natural pigment of dyes given intravenously, of blood-borne viruses, and of syphilis, is most pronounced. (If imperfect recovery from injury can not be invoked to explain the persistent permeability of the capillary endothelium in scar tissue, an alternative possibility is that the newly formed vessels have failed to arrive at complete maturity.)

The Readiness with which Colloids are Concentrated in a Particular Part Depends Largely on the Size of the Particles:

Inflammation: The most familiar cause of increased permeability of the vascular endothelium is inflammation, ^{re}wherever it occurs and whatever causes it, with inflammatory edema as a common result. The process is confined strictly to the area which has been directly stimulated, and does not involve the neighboring vessels. The essential element of inflammation is the direct response of those cells to which an irritant has been applied.

Anoxemia and Accumulation of Metabolites: Cerebral tissue is peculiarly sensitive to the deprivation of oxygen. Anoxemia rapidly increased the permeability of the cerebral capillaries. The point of escape of colloids and cells from the capillaries corresponds with the site of the lowest tension of oxygen in these vessels.

Variation of Hydrogen Ion Concentration: Reactions of the blood vessels to the pH of the blood depend upon the condition present at the time: when there is no accumulation of acid in the tissue, an increased alkalinity of the blood causes vasoconstriction, and an increased acidity causes vaso-dilation. But when acid has accumulated in the tissue, then an increase of alkalinity of the blood causes vaso-dilation, while acids have the opposite effect. In other words, with a constant alkaline pH of the blood, an increase of acidity in the tissues leads to vaso-dilation. Inflammation is accompanied by acidity. Cooling a limb increases alkalinity of the skin by reduction of metabolism. Warming increases acidity as does arrest of circulation. The physicians of 100 to 200 years ago used both these methods, warmth and arrest of circulation (compression), combined with various local applications and drugs administered orally for cancer of the breast (Tanchou, 1844).

Circulating Poisons: Poisons brought into direct contact with the vascular endothelium will reduce its resistance to permeation. Some venoms and toxins, either by direct injury or indirect influence, render the capillaries incompetent. A variety of organic and inorganic chemical reagents may have a similar effect.

Defective Constitution of the Blood: Quantitative defects in the components of the blood may be enough to cause an increased capillary permeability, (i.e., reduction of protein content). Amyloid disease is a recognized example of this cause of increased endothelial permeability.

Physiological Activity: Not a pronounced causal agent, but there is a definite and slight increase of endothelial permeability preceding or accompanying activity of an organ.

Immaturity, or Imperfect Recovery After Injury:

Vasodilation plays a minor part. It is not an essential factor in the causation of local edema; permeation is not prevented by vasoconstriction. Vasodilation may be regarded as an accessory though subordinant factor.

Transport of Matter from the Blood Stream to the Tissues by Production of Plethora and Venous Obstruction: Variations of hydrostatic pressure play a minor and almost negligible part. Venous obstruction acts in two ways: first by increasing the

permeability of the vessel walls, and secondly by the rise of intracapillary pressure.

Simple suction, however, intense, never produces wheals, even on susceptible skins. Applied over a developing wheal the increased venous pressure prevents the wheal from forming freely. At the site of cupping a complete stand-still of the blood develops.

Hyperemia: Dilatation of the arterioles, capillaries and venules with an increased flow of blood through them. Striking though it may be as an accompaniment to inflammation, hyperemia occurs apart from that condition and is accompanied by a different range of phenomena. Dilatation of the arteries in response to irritants was regarded by Lister as a functional phenomenon developed indirectly through the nervous system, whereas stasis was the result of the direct operation of the irritating agent on the tissues. The blood in hyperemia is well oxygenated and relatively free from metabolites.

Hyperemia unaccompanied by any condition causing an increase of endothelial permeability will not of itself bring about any considerable augmentation in the output of lymph. Yet it seems that an artificially produced hyperemia is capable of adding considerably to the volume of lymph derived in a given time from a limb, the permeability of whose vessels has been increased by some other cause.

A profound degree of transudation may occur in the absence of any hyperemia.

Changes in Hydrogen Ion Concentration: Fischer believed the chief factor in the causation of inflammatory edema was the increased imbibition of water by the colloids of the injured tissue, due to the presence of acids formed as a result of injury.

Inflammation causes not only an increase of the amount of lymph produced, but the lymph itself becomes richer in protein. Lewis has shown that the fluid of wheals contains all the proteins of the blood plasma.

Several investigators have found that inflammation is accompanied by acidity, the grade of which seems to have some relationship with the degree of inflammation:

centre of a furuncle	pH: 5.96
acute axillary abscess	5.98
phlegmonous abscess	6.05

acute emphyema	6.24
impetigo bullosa	6.44
chronic emphyema	6.57
coxitis tuberculosa	6.58 - 6.81
cold abscess	6.91 - 7.00
pleural exudate (?T.B.)	7.00
tuberculous ascites	7.03
pleural exudate (carcinomatous)	7.09
ascites due to morbus cordis	7.21
average of five healthy tissues	7.21

Electrophoresis: As soon as the endothelium of the small vessels becomes permeable from any cause, several forces hitherto held in abeyance come into effective action and under their influence colloids and suspended matter, including blood cells, will be transferred from the interior to the exterior of the affected vessels.

Electrical disturbances accompany trauma of living tissues, the injured surface becoming electro-positive in respect to the uninjured. There is now reason to believe that the diapedesis of colloids, free inorganic particles and organized bodies, including bacteria and leukocytes, is due mainly to electrical energy. (They all carry negative charges and are therefore attracted to any tissue which is relatively positive.)

The Size of Transported Particles: Size seems to have an important influence on their localization from the blood stream. Smaller particles localize more readily than larger ones, presumably because of lesser hindrance to their passage through the capillary endothelium. Colloidal dyes such as isamine blue and Congo red are more rapidly and intensively concentrated in inflamed tissue than coarser suspension of India ink or mercuric sulphide. Similarly, viruses are localized more readily by inflammation than are bacteria. A remarkable fact is the constancy with which *Treponema pallidum* finds its way into fields of irritation - and that it will pass through filters that will restrain most bacteria. The effective size of any organized structure cannot be gauged by its appearance when at rest under the microscope. If it were so, there would be difficulty in accounting for the early diapedesis of white

blood corpuscles. (They undergo great distortion when they pass through the capillary wall.) It has been suggested that the peculiar shape of the nucleus of the polymorphonuclear leukocyte is a special adaptation to facilitate the escape of the cell through the vascular endothelium.

The Electrical Charge of the Particles: The blood being alkaline, the inner surfaces of the blood vessels, the cells and colloids of the circulatory stream all carry negative electrical charges. Any substance therefore which is injected in large amounts into the blood must also bear a negative charge if it is to circulate freely, for positive substances so introduced will become adsorbed at once onto the walls of the blood vessels, and onto the electro-negative constituents of the blood. For this reason, perhaps, electro-positive substances given intravenously are apt to have injurious effects, and may in any case show little or no tendency to become concentrated in the macrophage system.

Von Jancso found that when arsenious acid in distilled water was given intravenously to rats it caused no damage to the reticulo-endothelial cells, but when adsorbed by India ink and so introduced it brought about reticulo-endothelial catastrophe in 13 hours. He was also able to poison the reticulo-endothelial cells with the electro-positive dye Janus green by adsorbing it to India ink. Though toxic for the animal, Janus green alone in watery solution does not become localized in the reticulo-endothelial system.

Spagnol stated that negatively charged colloidal dyes introduced into the blood stream always become localized in areas of skin where irritation is caused, but positively charged dyes never do, even in large doses. But if an electropositive dye is added to an electronegative one, the charge on the former is reversed and then it is taken up by the phagocytes of the reticulo-endothelial system.

Discussion: Life appears to consist largely of the maintenance of potential differences at the cell boundaries by a supply of oxygen on the one hand and by metabolic processes on the other. With cellular injury the conductivity of the intervening phase is diminished and the potential differences fall. With an increase of injury and conductivity the differences of potential will disappear and unless restored,

life will cease.

The Retention of Colloids and Other Substances by Inflamed Tissue: When plasma, fine organic particles, viruses, bacteria and leukocytes migrate into the perivascular spaces due to inflammation and certain other conditions, they do not drain away speedily in the lymph stream in the presence of established inflammation. The retention of transuded lymph is familiar to everyone as inflammatory edema and serous effusion; and the local retention of the polymorphonuclear leukocytes is also generally recognized, especially if the pathological disturbance has led to the formation of an abscess. The principle holds good for other matter than lymph and blood cells, such as dye and fine-colored particles.

"Opie, in a series of papers has discussed the arrest and concentration of antigens in inflamed tissues. He observed, while immunizing rabbits against egg-white or horse serum, that these substances, after repeated injection into the peritoneum or the subcutaneous tissues, entered the blood stream with decreasing readiness.

In well-immunized animals these antigens failed entirely to enter the circulating blood unless given in massive dosage. In a non-immunized animal, however, egg white and horse serum readily passed into the blood stream, where they could be detected by precipitin tests for seven, eight or nine days after their introduction into the subcutaneous tissues. He believed that when an antigen meets an antibody in the living organism an acute inflammation is at once produced in the tissues where they meet. This inflammation has the double effect of (a) preventing the free distribution of the antigen, and (b) causing a copious inflow of antibody owing to the increased transudation which results from inflammation. The Arthus phenomenon, thus represents a protective arrangement whereby an antigen is fixed and destroyed at its portal of entry.

"Okuneef (1924) observed that the absorption of trypan blue from the peritoneal cavity was delayed if animal charcoal, casein or gelatin were injected simultaneously with the dye or 30 minutes previously.

"In some further experiments he inquired into the effects of hyperemia and inflammation on the rate of absorption of a dye injected into the subcutaneous tissues

of the rabbit's loin. He found that vaso-constriction caused by a previous injection of adrenalin at the site of injection of the dye delayed its absorption. A rubber bag filled with ice applied to the loin for 45 minutes, the dye being injected within 5 minutes of applying the bag, also resulted in a delayed absorption of the dye. Heat, applied by a hot water bottle so as to preserve a temperature of 35 - 45°C. between the animal's skin and the bag, caused an increased rate of absorption. The same result followed hyperemia due to the application of a mustard plaster, the dye being injected within 10 - 20 minutes of applying the plaster. Experiments carried out with turpentine were of special interest: If a small amount of turpentine (0.06 to 0.2 cc.) was injected subcutaneously in the loin immediately before giving the dye, an increased rate of absorption occurred, but if the trypan blue was injected 12 hours after the turpentine, a great reduction occurred in the rate of absorption of the dye. (See charts 211-214 reproduced from Okuneef's paper)."

Burrows regarded these results as of considerable importance since they indicated the time interval requisite for the establishment of conditions favorable to retention. (These factors should be considered in planning the sites, dosage and frequency of toxin injections and whether to apply local heat to tumors to help localize toxin injected intravenously or remote from the tumor into other sites.)

Burrows noted that it is difficult to be sure when producing hyperemia by heat that the tissues have not been injured to the extent of producing an inflammatory reaction. His own experience confirmed that of Rogowicz in which, although a dye given intravenously appears in a larger concentration in hyperemic tissue than elsewhere, it shows little tendency to be retained there unless the stimulus causing the hyperemia has brought about inflammation also.

He also describes Menkin's experiments with induced aseptic inflammation in causing retention of dye in the inflamed areas.

In another experiment Menkin injected a small amount of diluted croton oil into the subcutaneous lymph space of a frog's thigh. After an interval varying from 45 minutes to 24 hours, he injected .05 cc. of 1 per cent solution of trypan blue into

the inflamed portion of the thigh, and made a similar injection into the same part of the thigh of a normal frog. After several hours both animals were pithed and examined. In the control frog the dye had diffused through the body, staining the buccal cavity, tongue, abdominal wall and thighs, viscera and heart. The experimental frog, however, showed intense staining at the site of inflammation, no dye elsewhere.

Regarding the rapid dissemination of bacteria in normal animals, Noetzel observed that *B. pyocyaneus*, when injected into the knee joint of a rabbit, could be demonstrated in the inguinal lymph nodes within 10 minutes or less. Buxton and Wells and Johnstone recorded that bacteria injected into the peritoneal cavities of normal animals reached the blood stream via the lymphatics within a few minutes.

Schmidt-Ott noted that trypanosomes, spirochetes, and certain bacilli may be found within the regional lymph nodes within a few minutes after their subcutaneous inoculation, and he believed that rapidity of dissemination to the lymph nodes was not dependent on size, motility or virulence, but that as regards the entry of organisms into the general blood stream, virulence played a decisive part.

Pawlowski (1909) found that if a suspension of *Staphylococcus aureus* were injected into the knee joint of a guinea-pig, in which inflammation had been produced four days before by introducing turpentine, dissemination of the organism was delayed or entirely prevented.

Similarly Sicard, Paraf, and Wallich (1927) found that an aseptic peritonitis produced by an injection of tapioca prevented the dissemination of cholera vibrios and other organisms introduced into the peritoneum.

Opie (1920) states that streptococci introduced into the peritoneal cavity of healthy rabbits enters the blood stream in a few minutes; whereas the presence of aseptic peritonitis set up by an injection of aleuronat 48 or 72 hours before, entirely prevented the organisms from becoming disseminated.

Willis's (1925) experiments with inoculated tuberculosis are also cited.

A striking example of the retention of fine inorganic particles in tissues which are the seat of chronic inflammation is anthracosis: Cummins and Sladden (1930) showed that no remarkable degree of anthracosis occurs in coal miners unless silica

has also been inhaled. In the absence of inflammation set up by the presence of silica, the relatively non-irritating coal dust is not retained in the lung in amounts comparable to those which are so retained in the presence of silicosis.

The Causes of Inflammatory Retention:

An Increased Osmotic Pressure in the transuded material may be one reason.

Stasis of Lymph: Still hypothetical Burrows believed.

Clotting of Lymph: Sufficient to block natural flow. Menkin made careful studies into this matter. He brought about cutaneous inflammation in a rabbit by introducing a culture of *Staphylococcus aureus*. After a sufficient time he injected 1 cc. of a 1% solution of trypan blue into four or more areas of skin adjacent to the site of inflammation. The inflamed area became circumscribed by a band of blue, the dye failing completely to penetrate the edematous tissue. He performed similar experiments on frogs, causing local inflammation by means of diluted croton oil and subsequently injecting a solution of trypan blue into adjacent areas. No dye diffused into the inflamed part. Menkin attributes this to the occlusion of lymphatic vessels and the presence of a network of fibrin in the inflamed area and he regards the fixation of foreign substances by the inflammatory reaction as due to mechanical obstruction caused by a network of fibrin and by thrombosed lymphatics at the site of inflammation.

Menkin records that *B. prodigiosus* (*Serratia marcescens*) injected into inflamed tissue is fixed there and fails to disseminate to the regional lymph nodes as readily as when injected into normal tissue: this organism inoculated at the periphery of an inflamed area does not readily penetrate into the site of inflammation. These experiments, he believes, furnish additional evidence that the fixation of foreign substances by the inflammatory reaction is primarily due to mechanical obstruction caused by a network of fibrin and by thrombosed lymphatics at the site of inflammation. (This would seem to explain why in cases treated by intramuscular injections of Coley toxins the sites of inoculation became very indurated (localizing the toxins in these sites) and the effect on the tumor was much less marked than when using intratumoral or intravenous injections.)

Phagocytosis: plays an appreciable part in the retention of bacteria, dyes and other substances in inflamed tissues. Falk and Matsuda have observed that phagocytosis of bacteria is largely influenced by the electric charge which they carry, and that it is possible to effect alterations of this charge by artificial means; and Falk advanced the view that virulence of micro-organisms is dependent upon their electric charge.

Agglutination of Bacteria in Vivo: Immunity Factor with regard to the fixation of a foreign protein under the influence of an immune response it may be, as Opie (1925) suggested, that specific precipitation plays a part.

Electrostatic Condition in the Tissues: (Precise data are lacking.) Inflamed tissues may be positively charged relative to normal tissues. Inflammation being accompanied by an increased permeability of the blood-vessels and by an augmented difference of electrical potential between the contents of the blood vessels and the extra-vascular tissues, would not only result in the transference of the mobile electronegative colloids of the blood to the positively charged tissues but until neutralization of the charges had taken place to some extent, the effused substances would be held within the damaged zone by electrical attraction.

The Electrical Charges on the Particles which are Retained under the influence of inflammation must be of importance if the foregoing theoretical argument is sound. On such a basis it is easy to account for the rapid spread of negatively charged bacteria through non-inflamed electro-negative tissues, as it is to understand their retention in inflamed tissue under the influence of the raised electrical potential. The same argument can be applied to the retention of proteins, acid dyes and other electro-negative substances under the influence of inflammation.

The Inflammatory Barrier: Every surgeon is aware of its potency in limiting the spread of micro-organisms. Apart from surgical operations, the routine treatment of a local infection consists entirely of attempts to second Nature's inflammatory response.

Durham showed that the resistance of the peritoneum against infection could be greatly increased by preliminary production of an aseptic peritonitis. (Pozzi's famous case (1878, 1904) is of interest in this connection. He induced peritonitis by injections of iodine in a case of advanced ovarian cancer. See below Page 169.)

Besredka (1923) learned that animals could be protected against a local dermic inoculation of anthrax by previously injecting into that part of the skin some filtrate from a culture of the organism or by applying the filtrate to the skin by means of a compress. He later found that by comparable means a local protection could be produced against staphylococcus which was virulent for guinea pigs. He further observed that a filtrate made from an 18-day broth culture of this staphylococcus was non-toxic when injected into the animal. Staphylococci inoculated into the filtrate maintained their vitality but did not multiply. When the living organisms were inoculated subcutaneously together with some of this culture filtrate the resulting lesions were not so severe as those produced by the staphylococci minus the filtrate. He obtained similar results with streptococci and their filtrates.

He and Urbain obtained a local protection against a virulent streptococcus by previously dressing the skin with bacterial filtrates. Besredka believed that the local immunity was brought about by the presence of specific inhibitory substances in the bacterial filtrates and therefore applied the method in the treatment of puerperal sepsis and other human infections.

Brocq-Rousseau, Forgeot and Urbain confirmed the possibility of obtaining local immunity in guinea pigs against intradermal injections of a virulent streptococcus by previous inoculation with a culture which had been attenuated by heating to 60°C. for 15 minutes.

Burrows believed that in view of more recent work it was doubtful whether the effect of these bacterial filtrates was to any great extent the consequence of specific anti-bactericidal properties, but rather to stimulating a non-specific resistance.

Gratia found that the previous application of vesicants made the skin more resistant to infection and this protection lasted about two weeks. Mallory and Marble produced a local cutaneous immunity in rabbits toward staphylococcus equally readily by means of sterile filtrates of cultures in broth and sterile broth alone. The immunity was strictly local, and was manifest within eight hours, and lasted for 15 days at least. The protection obtained by the bacterial filtrate was never greater than that obtained by the original broth, from which the filtrate had been prepared. Miller

found that guinea pigs were protected locally against staphylococcal, and rabbits against streptococcal infection by previous treatment of the skin with horse meat broth or beef tea, or with bacteria-free filtrates of cultures. He regarded the immunity as non-specific. Protection appeared in 24 hours, lasting 10 days. He noted that if inflammation was too severe, no increase of resistance was obtained. Freeland and Toomey also found plain broth as effective as specific broth in protecting guinea pigs against subcutaneous injections of staphylococcus.

Other pathologists, while admitting the potency of non-specific protection, have obtained a still higher degree of local immunity by the use of specific serum or broth. Gay and Morrison called attention to the leading part played by the macrophages assembled as the result of aseptic inflammation. They noted the results of injection of streptococci into the pleural cavity of rabbits after the onset of inflammation caused by various substances, and they found that meat infusion broth and diluted egg white, which in 24 hours had produced a notable increase of macrophages in the cavity, protected the animals against 100 times the minimal dose that was fatal for untreated rabbits. Substances which when injected into the pleura brought about a large increase in the number of polymorphonuclears but not a pronounced increase in macrophages, were not effective in affording protection to the host. Thus an injection of 5% aleuronat in 0.3 sodium chloride gave these "absolute counts" (in millions): macrophages 3.8, polymorphs 58.9, and no recognizable protection. With strong broth injection the exudate contained: macrophages, 18.7, polymorphs, 47.9 and complete protection. Nakahara came to a similar conclusion. He was able to greatly enhance the resistance of the peritoneum in mice against certain organisms by 48 hours previously injecting into the abdominal cavity 0.2 cc. of commercial olive oil. At first this causes an exudation of polymorphs, but at the end of 48 hours these become replaced with macrophages. The protection gradually subsides in the next two weeks. He used *Escherichia coli*, *Staphylococcus aureus*, and a pneumococcus.

Gay and Clark (1924 and subsequently) found that normal rabbit serum injected into a rabbit's pleura produced just as high a macrophage count as antistreptococcal rabbit serum, but the latter led to an earlier sterilization of the pleural cavity

after its infection with streptococcus. (Macrophages reached their maximum earlier with immune serum.) Rivers and Tillett also observed that immune serum was more efficient than normal serum or beef broth in protecting the skin of rabbits against streptococcal infection.

Thus it is seen that to provide the most efficient barrier against infection it is not enough merely to cause a local inflammation, but the correct type: (a) i.e. the maximum number of macrophages must be mobilized in the zone of infection. (b) the level of local immunity must be raised by specific treatment, (enabling the tissues to produce agglutination of the invading organisms). (c) the degree of inflammation must be appropriate.

Hanger noted that severe injury of the tissues by chemicals or an excessive antigen-antibody reaction produces loss of local resistance even in immune animals. Mild injuries from the same causes, however, have a protective effect. Miller (see above) also noted this.

Halley, Chesney and Dresel showed that while fresh wounds in rabbits were susceptible to infection with *Streptococcus erysipelatis* and *Staphylococcus aureus*, granulating wounds were resistant to these organisms, but this resistance of granulating wounds was not general against every infection. (*Pasteurella* applied to granulations gained access to the blood and killed the animals.) Inflamed tissue forms a nidus that is especially favorable to the growth of tubercle bacilli, (i.e. silica). The grade or type of inflammation must be considered because although local injections of calcium chloride or turpentine caused more severe inflammation than silica, it was not so favorable to the growth of tuberculosis.

Viruses also become localized in inflamed tissues (amply proved).

A barrier of granulations will act as a buffer against the absorption of a toxin. Noetsel found that in rabbits and in guinea pigs the time required for a wound surface to become resistant to bacterial infection was five or six days. (Comment: Thus toxin therapy should be started before or immediately after operation in order to permeate the entire area before scar tissue is formed.)

The protecting barrier of granulations requires in certain of the lower animals a period of several days to develop, and even a slight injury just enough to cause bleeding may lay open the defenses to bacterial or viral invasion.

The production of a macrophage barrier in healthy subcutaneous tissue or in the peritoneum or pleura takes 24 hours at least and is effective for a week or two.

Burrows stressed Okuneef's experiments with the absorption of dyes noting that hyperemia accelerated absorption and that a definite lapse of time was required to institute these conditions which cause retention of substances under the influence of inflammation.

Persistent Permeability: (Chapter XV, p. 244) A diminution of alkalinity or increase of acidity is the usual accompaniment of damage to the tissues and as long as excessive acidity continues it seems that any contiguous capillaries will be deprived of their normal tone.

Whealing cannot be induced again in the same area of skin for some time.

An increased exudation from the blood vessels takes place continuously in the presence of pyogenic infections or of other persistent causes of irritation (i.e. turpentine in a fixation abscess) whereas, with non-septic and discontinuous traumatism, periods of time intervene during which little or no exudation takes place from the blood vessels into the injured part.

The Inflammatory Response: Roger divided the sympathetic nerve of a rabbit's ear and inoculated both ears with equal quantities of *Streptococcus erysipelatis*. He found erysipelas developed much more promptly in the hyperemic ear than in the normal one. In the next two or three days erysipelas developed in both, always more pronounced in the denervated one. However, from the third to fifth day the ear with intact nerves became the seat of a severe lesion, while the other one had become nearly normal.

A full supply of well-oxygenated blood has the effect of increasing inflammatory exudation.

Variations in pH may be the chief agents in regulating the inflammatory response.

Therapeutical Considerations, The Curative Use of Hyperemia: (Chapter XVI)

From ancient times measures to increase the local blood flow have been used therapeutically. Hippocrates used fomentations and placed actual cautery as among the most potent of remedies. More recently diathermy, fomentations, dry heat, tincture of iodine, and other chemical rubefacients and liniments, also setons, blisters, fixation abscesses and cauteries are used. The general appreciation of these agents and the selection of the one most suitable for an individual case, have both rested, till recently almost entirely on empiricism, tradition and convenience.

There is a sharp and primary distinction between measures which cause hyperemia alone and those which induce inflammation.

Hyperemia stimulates healing of wounds: It should be avoided in tuberculosis. It may also favor the development of syphilis.

Therapeutic Values of Artificially Induced Inflammation: It may be induced (a) as a means of producing an accessory hyperemia in the neighborhood of a diseased focus, (b) to forestall the establishment of infection in a freshly inoculated healthy tissue, (c) to prevent the spread of established infection by the creation of an antibacterial barrier around the focus, (d) to bring about the local fixation and destruction of micro-organisms which are free in the circulating blood, (e) the localization of pharmaceutical remedies within diseased tissues. (This applies to toxin therapy. In tissues that have been heavily irradiated it would seem feasible to initiate an aseptic inflammation within the zone of an intended operation - so as to increase the macrophages which have been destroyed by the radiation.)

The temporary irritation caused on wound surfaces by antiseptics - far from being inimical to healing, may favor the process. Carrel concluded that irritation expedites healing of skin wound^s, and that onset of repair is delayed in a wound that is not irritated.

The Local Fixation and Destruction of Micro-Organisms Present in the Circulating Blood: Inflammation not only prevents dissemination of infection but may have remedial value once dissemination has occurred, since an inflammatory focus will segregate micro-organisms from the blood stream. This is the principle underlying the treatment

by fixation abscess, cautery or other therapeutic measures involving the establishment of an inflammatory focus for the cure of a general blood infection. Moreover, matters other than bacteria can be localized by an abscess.

Although the curative effects of cutaneous inflammation appear to have been recognized empirically from the dawn of history, they receive little attention now.

Jenner, in a letter to Charles Henry Parry (1822) on the influence of artificial eruptions, not only expresses his own belief in the therapeutic value of cutaneous irritation, but refers to similar opinions expressed by his contemporaries and predecessors. His explanation is that an inflammation of the skin diverts disease from other parts of the body.

The only known method of localizing bacteria from the blood stream is inflammatory fixation. There is no alternative method.

Laboratory work has shown that if bacteria are injected into the blood stream of an animal in which an abscess has been induced, some of the bacteria will find their way into the abscess. This fact confirms the judgement of Jenner, Fochier and others in causing cutaneous irritation and fixation abscesses for the treatment of mankind. However, these methods are not generally viewed with enthusiasm by clinicians today.

The readiness with which particles undergo diapedesis appears to depend largely on their size: a mustard bath which may be sufficient to localize viruses in the skin may yet be too mild to fix bacteria owing to their greater dimensions. Bacteria may require a mustard poultice to localize them. Much experimental work must be carried out before a high degree of therapeutic success can be expected from this form of therapy.

Nobody will suppose that fixation abscesses can segregate all the micro-organisms circulating in the blood. The liver and spleen will still retain a large proportion. Nevertheless, if given sufficient time, a fixation abscess will take and hold some of the circulating bacteria and thus may relieve the assault made on the reticulo-endothelial system. Not only does a fixation abscess collect bacteria from the blood, but it also destroys them.

The Use of Inflammation to Localize Pharmaceutical Remedies Awaits Further Exploration. Since a sterile inflammation can be set up at will in any part of the body, it seems almost certain that with this method we can localize any substance that can be prepared in the necessary physical state in whatever organ we wish by introducing it into the blood stream. Its deposition in the tissues will be largely within the macrophages, though not always entirely so. Even so a medicament may be effective. Colloidal substances with particles that are not too large and which carry a negative electric charge, will with certainty escape from the blood vessels (when injected intravenously) and reaching extravascular regions will be retained there in a relatively high concentration. Burrows reiterated that he believed we can obtain a special concentration of any substance we choose in an inflamed tissue provided we introduce it to the blood stream in the form of an electro-negative colloid whose particles are of suitable dimensions. As a rule there will be no difficulty in effecting the necessary aseptic inflammation if it is not already present.

General Summary and Conclusion:

Three conditions are required for the localization of many blood borne diseases - namely:

1. An abnormal permeability of the walls of the small blood vessels.
2. The presence of forces which will transport the noxious agents through the endothelial cytoplasm.
3. The retention of noxious agents in the tissues under the influence of inflammation.

He noted that these three conditions lead to the localization not only of the agents of disease, but to the factors of defence. (Burrows, 1932)

An interesting example of the effects of trauma in localizing blood borne bacteria occurred in 1892 in a patient under W. B. Coley's care, a male aged 46 with a recurrent inoperable sarcoma of the back with metastases in the groin. Coley attempted to induce erysipelas in this patient by inoculations of fresh cultures of streptococci made directly into the tumors. Finally after four weeks he succeeded in doing so with a fresh culture. Coley reported: "From the beginning of the attack the change that took place in the tumor was little short of marvelous. It lost its lustre and color, and had shrunk visibly within 24 hours. During the early part of the inoculation treatment (before erysipelas developed) the patient "received a blow on the chest while scuffling with another patient. Four weeks later, when recovering from the erysipelas he began to feel pain in the region of the injury and soon a diffuse swelling appeared." The temperature ranged from 101° to 102.5° F. for a week, and a large abscess developed in this area from which 10 ounces of pus were evacuated. The tumors disappeared following the infection but recurred and again regressed following toxin therapy. Final reactivation with ascites caused death 10 years after onset and four years after erysipelas developed. (W. B. Coley, 1893, Case VI; 1894)

Fisher and Fisher (1967) studied the effect of trauma on localization of tumor cells. They concluded that increased numbers of tumor cells lodge at sites of trauma, and may well be the reason for the observation of augmented metastases. They added: "The hazards of translating findings from an experimental model to events which may occur in man are fully appreciated, yet to disregard the evidence relating trauma to metastases as being inconsequential appears equally inappropriate. There are many clinical observations that surgery, chemotherapy and even irradiation (all forms of trauma) may augment metastases. Such modalities may change host-tumor relationships allowing for unexpected neoplastic growth. In this regard surgeons have long practiced self incrimination for local recurrences of tumor following 'adequate' operation when actually these recurrences may have been the result of a biological phenomenon beyond their control, i.e. circulating tumor cells lodging at a site of trauma."

Agostino and Cliffton (1965) also reported on trauma as a cause of localization of blood borne metastases and discussed the preventive effect of heparin and fibrinolysin.

Lohmann (1931) discussed the physiology of tumor cells and various therapeutic attempts at producing conditions within the body which may interfere with tumor growth, their respiration and glycolysis.

Ehrlich found that a tumor which had been implanted in mice did not grow or regressed rapidly (acquired tumor immunity) if the animals had been treated with diluted tumor material or if they had suffered an infectious disease, e.g., relapsing fever: the transplants failed completely in a series of animals.

Inflammatory Reactions: "Kempner and Peschel (1930) observed that, corresponding to the extent of an inflammation, the inflamed tissue separates itself from the normal tissue and starts a life of its own in the area of inflammation. The metabolism of inflammation is the center of this life. The metabolism of the inflammatory cells is a noxious metabolism of necrosed cells, with considerable respiration and glycolysis; it causes in the inflammatory fluid:

reduction of oxygen

increased lactic acid

increase in CO_2

reduced bicarbonate

reduced sugar

lowered pH.

"Based on these observations, one should assume that the inflammatory state of tissue may offer the worst conditions for the life and growth of malignant tumor cells, and it might perhaps be possible that tumor cells would perish under such conditions.... For the optimum of the glycolic efficacy of the tumor cell is linked with alkaline reaction and depends on the bicarbonate contents - the reaction in an inflammatory area is acid, the bicarbonate contents are reduced 60%. The metabolism of a tumor cell in an inflammatory fluid should, therefore, differ from that in a normal body fluid, such as lymph or blood serum.

Experiments on the Influence of Inflammation on Tumor Metabolism:

Method: Respiration and aerobic glycolysis of tumor cells were determined in human serum and in inflammatory fluids of man, by using the contents of cutaneous blisters, which were produced by cantharides (a counterirritant and vesicant) and pleural exudates. Sections from Jensen's rat sarcoma and human spontaneous carcinoma were used as tumor cells.

Sterile puncture of the inflammatory fluid was carried out after the cantharides plaster had exerted its effect for 24-48 hours (the age of the pleural exudate could not be exactly determined) the cells were centrifuged and the fluid saturated with various gas mixtures at 37.5°C . (99.4°F .)

Results: Aerobic glycolysis of the tumor cells is always reduced considerably in the inflammatory fluid as compared to serum. The aerobic glycolysis of tumor cells had almost completely disappeared in inflammatory fluids obtained from healthy human patients after about 50 hours' duration of the inflammation: i.e., the tumor cells no longer showed the specific tumor metabolism in the inflammatory environment, but showed that of normal tissues. It was shown that the tumor cells are destroyed in the inflammatory fluid if the latter is allowed to exert its effect on the tumor cells for a sufficiently long time.

Sections of rat sarcoma were again placed in normal serum after a sojourn of 6, 10 and 14 hours in the inflammatory fluid; their metabolism was then determined; not only the aerobic glycolysis but also the respiration was considerably reduced after being exposed to the inflammatory fluid for six hours. After 14 hours in the fluid, respiration and glycolysis was zero, i.e., the tumor cells had undergone necrosis, while the tumor tissue which had been maintained in normal serum under constant conditions, still presented its original metabolism.

Thus, inflammation is capable of causing the death of the tissue of malignant tumors within 14 hours, even in the presence of optimal saturation of inflammatory fluid with oxygen.

Hypothesis Concerning Origin of Tumors and Possibilities of their Treatment: It has been demonstrated that non-specific inflammatory reactions which depend on the metabolism of inflammatory cells (oxygen, sugar and bicarbonate deficiencies, acid reaction) are capable of destroying tumor tissue within 10-14 hours. The inflammatory capacity, however, depends on the general health of the total organism and of the single organs in each case, and decreases with advancing age.

Not only one "malignantly degenerated" cell is required to produce cancer but also the "incapacity of the tissue for inflammation." The rapidity of tumor growth is determined by the relation: amount of degenerated cells v. inflammatory capacity of tissue affected.

The inflammatory capacity does not signify only the intensity of the inflammation, but also the sensitivity to any minimal change in the normal tissue which is indispensable for eliciting an inflammation, irrespective of whether this change depends on a mechanical injury, on bacteria, on degenerated cells or on any kind of noxa which may cause simultaneous degeneration of cells. Thus just the weakest stimuli may become the most dangerous ones with respect to the genesis of cancer. An insignificant noxa may elicit the malignant degeneration of cells but, in the presence of reduced susceptibility of stimulus in the affected tissue. . . may not induce sufficient protective inflammatory reactions.

In conclusion Lohman suggests that in addition to combatting the noxa which may cause a degeneration of body cells, and to destroying these degenerated cells by surgery, radium or tumor-destructive substances, one should preserve the inflammatory capacity of the body, so that every degenerated cell may be destroyed at its origin by isolation, starvation and acid and to combat the degenerated cells by intensifying the inflammatory capacity to a maximum and by mobilizing these increased inflammatory reactions for the affected tissue. (Lohmann, 1931)

The experiences of two French physicians, Magnant (1891) and Bayle (1903) using injections of inflammatory exudate^s, the former heterologous, the latter, homologous, suggest that such treatment may stimulate resistance in patients suffering from chronic or debilitating diseases or that it may speed wound healing.

Magnant (1891) reported on his therapeutic use of inflammatory exudates (or "human lymph" as he called it) in the treatment of pulmonary tuberculosis. He noted that this material was obtained from the blisters produced by vesicants (cantharides).

He stated that atonic ulcers and unhealthy wounds healed under the influence of injections of inflammatory exudates obtained from healthy individuals. Also, infectious diseases, such as tuberculosis, typhoid fever, etc., were successfully controlled by this method. He added: "Even cancer recedes under the influence of a 'revivifying lymph'".

The injections of inflammatory exudates, in localized chronic affections, produces astonishing results: a vast varicose ulcer of the leg, resistant to the most varied treatment for several years, healed completely in less than a month after four injections of 1 gram each of the inflammatory exudate.

An enormous cervical lymph node in a phlegmatic young girl "melted away as if by magic," after a single injection. In another case, the fluid was introduced by Pravaz's syringe directly into the glandular tissue of the breast. There resulted an inflammation (suppurative) which terminated by a melting of the gland as in an ordinary cold abscess.

Magnant suggested, however, that it was more rational to inject the material according to the lymphatic channels in a given area, directing the injections of the superficial tissues toward the deeper organs, to facilitate penetration and absorption of the therapeutic fluid through the lymphatic system. (Magnant, 1891)

Bayle (1903) produced a small area of vesication on the normal skin of the arm of a patient with a very advanced, inoperable cancrroid. He then aspirated the inflammatory exudate and injected it into different parts of the tumor. After only two or three injections, repeated at intervals of eight days, a notable change was produced.

Bayle believed this was a new principle of serotherapy, applicable not only to skin cancer, but to those of other organs. He added: "I injected the fluid into the tumor, but I don't know whether subcutaneous injections of the same fluid in other sites might not have produced the same effect."

He mentioned briefly various forms of serotherapy which had been tried in Europe the previous year by Von Leyden and Blumenthal, Charcot, Richelot and Wlaeff. These men injected emulsions of cancer tissue into animals and used the serum from these animals to treat inoperable cancers. Some cases appeared to be ameliorated. However, these serums caused toxic side effects, such as fever, nausea, vertigo, and skin eruptions.

Altogehter different was the idea of Korlech who, noting that cancer occurred only in the aged, tried treating cancer patients by injecting serum from young individuals. Bayle mentioned the work of Coley in America as being a modern application of "érysipèle curateur" (curative erysipelas).

He then gave a detailed history of a case of very advanced, hopelessly inoperable, ulcerated cancrroid of the face with involvement of both orbits, the nose and the cheeks, in which injections of inflammatory exudate caused a very marked improvement: regression of the tumor and healing of the ulceration. The history has been abstracted in detail: (Bayle, 1903; cited by Vidal, 1910)

Diagnosis: Very extensive inoperable epithelioma involving the nose, both orbits and both cheeks, causing blindness of one eye.

Previous History: Mme. M., female, aged 72, widowed milkmaid. The patient's father had died at 70 of emphysema and chronic bronchitis, he also had rheumatism. Her mother died at 65 of unknown causes. The patient had eight siblings, all living and well. She was married at 18, and had six children and one miscarriage. She did not remember ever having a single illness. Onset, about 1889, a small "wart" appeared at the level of the root of the nose. This was "burned off". The tumor recurred and progressively enlarged, although it remained torpid, being confined to the root of the nose for a long time. Then suddenly it began to increase in size and at the same time deep induration extended toward both orbits and onto the upper cheeks. Ten years after onset the patient was struck on the center of her forehead by the horn of a cow. Following this an ovoid almost spherical tumor mass formed at the site of the injury, which progressively increased in size. This tumor did not appear to have any relation to the epithelioma. Bayle believed that the frontal tumor was of periosteal origin. About 11 years after onset of the epithelioma and a year after onset of the frontal tumor two small sinuses appeared on either side of the frontal mass and these suppurated. At this time the tumor involving the nose became ulcerated, exposing the naris, and the right eye which had been gradually invaded by the neoplasm, entirely disappeared, being compressed and thrown back by encroaching cancerous tissue. Finally, during the months prior to consulting Bayle, the left orbit began to be involved. When first seen by Bayle, the dorsal surface of the nose was completely ulcerated, with the left nostril laid bare by the tumor process. On either side of the nose indurated masses of tumor of the consistence of carcinoma extended very far out on the cheeks, with a few crusts covering the ulcerated surfaces having the typical aspect of carcinoma. The ulceration

extended from the open naris to the bleeding, irregular hard carcinomatous granulations, which had invaded the right orbit. The latter was absolutely filled and covered with tumor tissue, so that it was impossible to tell whether the eye still remained beneath the growth. Another extension of the tumor had invaded the left orbit as far as the cornea.

Preliminary Systemic Treatment: For 20 days the patient was given specific treatment with mercury and iodide of potassium without any amelioration being evident. Then for another 15 days large doses of quinine were given (Jaboulay's method) again without any effect being noted.

Inflammatory Exudate: Bayle then produced an area of vesication a few centimeters in diameter on the patient's arm, from which he withdrew about 1 cc. of inflammatory exudate. This he injected first in one part of the tumor and on other occasions in two different areas of the skin cancer. A total of eight injections were given at intervals of eight days. The only other local treatment consisted of washing the ulcerated areas twice a week with lukewarm boiled water to which had been added a small quantity of oxygenated water, 1 to 12 dilution. After drying, the area was powdered with sterile talc. At the time of the second injection, eight days after the first, the amelioration was such that the patient and her family were impressed. The induration of the lateral portion of the nose had diminished considerably, the neoplastic granulations had changed aspect, and begun visibly to regress, and even to ameliorate. Following the second injection a clear border of cicatrization formed on the ulcerated tissues and the right eye, which was shapeless, "squeezed," opaque, began to free itself "from the carcinomatous bars of its prison." At this time Bayle took his first photograph of the patient. Thereafter, little by little the improvement continued and the tumor masses receded from the orbit leaving the eyeball rather loosely attached, somewhat "like the clapper of a bell." All the ulcerated areas healed except for a few rare fissures which drained a small amount of fluid. The left eye was completely delivered of the tumor mass which had begun to invade it. During this time no injections had been made into the tumor of the frontal region, and this mass was not modified at all. It was partly hard, partly cystic, and "seemed to have nothing in

common with the subjacent skin cancer as regards etiology." Bayle made an exploratory puncture into one of the cystic areas of the frontal tumor and obtained a brownish colloidal fluid. Photographs taken by Bayle show that this mass was about the size of a large orange, protruding from the forehead about 7½ cm.

Clinical Course: Bayle cited this case briefly in February 1903 and in detail in May 1903, so that the final result is unknown. The marked benefit derived as regards healing and regression of the cancrroid suggests that inflammatory exudate from vesicles should be tried in ulcerated and inoperable cases at the present time, alone or in combination with other methods of treatment. It is of interest that the frontal mass did not appear to be influenced by the concurrent regression of the epithelioma. (Bayle, 1903; cited by Vidal, 1910)

Ungar (1953) discussed the evidence in favor of the view that patients who tend to have acute inflammatory episodes and infectious diseases have a low incidence of cancer.

He cited Von Bergmann as stating: "Even in respect to carcinoma, we shall, as do the ancients, have to raise the question anew whether some reactive inflammatory process might not injure the cancer cell, might not combat cancer. . ."

In 1910 R. Schmidt pointed out that in the histories of cancer patients infective diseases, and especially children's diseases are found much more seldom than in those of other patients: among 291 carcinoma sufferers he found 99 who had never at any time contracted any infectious disease. Schmidt then, in his private practice and in his capacity as head physician to two university hospitals followed up this phenomenon for several decades, with the result that 37 years later, in 1948, he was once more able to draw attention in his book, "Therapie und Prophylaxe innerer Krankheiten" (Therapy and Prophylaxis of Internal Diseases) to the fact that where marked "diathesis inflammatoria", as he termed it, existed cancer was a rarity. In 1931 Engel of the No. 2 Surgical Clinic of Vienna University reported that when the medical histories of patients were accurately recorded it was found that among 300 patients suffering from other diseases there were 16 who had never had an infectious disease but 113 such among 300 cancer patients. In 1937 Schier in his book on children's diseases, also confirmed Schmidt's experience.

Incidentally, it had also struck Schmidt that the vaccination of cancer patients against smallpox led much less frequently to the formation of pustules. Christoph U. Linder (New York) has now recently reported, on the strength of 20 years' experience, that poison ivy (*Rhus toxicodendron*), and which, similarly to the *Urtica dioica* and *Urtica urens* varieties of stinging nettle but to a much more pronounced extent than these, provokes most severe dermatitis in the majority of subjects and especially in allergics, generally provokes either weak skin reactions or none at all in cancer patients.

Henschen also, in his many years of practice as a surgeon (as he frequently em-

phasized in his lectures), reported similar experience in this field to R. Schmidt, and as a result he invariably instructed his assistants to compile the histories of patients with the greatest accuracy as regards children's ailments and infectious diseases. It was for this reason that the case histories of the Basle University Surgical Clinic from 1927 to 1945 were able to provide Ungar with the basic material for his investigations into this question.

From these 68,385 case histories, 4,192 of which related to cancer patients, it was ascertained that even when comparing the various decades of life, etc., the number of infectious and children's diseases which the non-cancer patients had experienced was on the average three times as high as in the case of the cancer patient. . . What Schmidt had called the infection index (number of infectious diseases contracted by the individual patient) had to be considered not only quantitatively, but qualitatively as well. For in this connection there is, for instance, a vast difference between a patient who has scarlet fever accompanied by intensive exanthema and high fever and one who has no distinct symptoms of disease, which is not recognizable as scarlet fever until later when desquamation takes place.

"For this reason we attempted to the best of our ability to obtain quantitatively and qualitatively accurate records of the 'diathesis inflammatoria' of all our inpatients in the year 1946 and the result clearly shows that this inflammatory diathesis was generally much weaker in cancer patients than in the majority of the others. . .

"It was observed in a small number of patients that, where cancer sets in, notwithstanding a relatively pronounced tendency to inflammation, the case is generally one of especial malignancy. By and large, however, Billroth's well-known dictum was confirmed: "It is as though a surplus of health appertained to the acquisition of a carcinoma."

Comment: In view of the importance of these questions it is most desirable that hospitals should collect further statistics of this nature. In areas where there are still family physicians in the old sense, these general practitioners can assist in a most valuable way, since they, thanks to their closer contact with the patient and his family, are often better aware of such a "diathesis." (Ungar, 1953)

Preble (1923) also studied this problem. He stated: "The immunities toward cancer in all or some of its forms are so manifest and manifold that in theory we ought to be able to arrive at some conception of the nature of the affection."

He searched for a common trait in various "immunes" - that is children, American Indians living on reservations, and lepers. These three groups have been shown beyond doubt to be comparatively free from cancer. . .The Indian. . .shares his immunity with other aboriginal and primitive peoples, so that it cannot be specific. The leper does not attain the cancer age (so the low incidence in lepers might be due to that).

Wetterer, believing that the body of the young human being contains a normal protecting substance, has sought to test the effects of injecting the normal serum of children intravenously in cancer patients. He reports several striking results.

Preble noted: "We know that types which seem immune to cancer as a whole cannot resist certain forms of the disease due to continuous irritation; betel chewers' cancer, bilharzia cancer of the bladder, and kangri burn cancer, (All occurring in regions where cancer incidence is otherwise extremely low.)

The immunity of the leper is real and not apparent. Hardly a single well-authenticated case could be found. "We can only surmise that some substance forms in the blood of lepers which is hostile to the development of cancer. This fact is not isolated or singular, for there is an entire series of data of the same type which come under the head of anti-biosis. In some cases we see cancer become arrested or even disappear under an attack of typhoid fever.

". . .Many (cancer patients) seem to possess defensive forces against the attacks of ordinary disease germs. They do not even contract the ordinary diseases of childhood and are wont to say that they have never been laid up as the result of illness. . .Certain statistics compiled in Sweden showed that a large majority of cancer victims had been partly or wholly immune to ordinary germ diseases. It is even possible that one sort of immunity excludes the other. The antibiosis of. . . cancer and tubercle is quite as remarkable as that between cancer and leprosy. Even

syphillis, despite many assertions to the contrary, plays a very slight role in the spread of cancer, and symbioses between these two diseases are extremely rare. The aboriginal with his immunity to cancer is badly ravaged by tubercle, syphilis and most of the other germ diseases. . .measles, influenza. (In the tuberculous, cancer, which is infrequently seen at best, runs a comparatively mild course.). . .

Something of the nature of antibiosis must be invoked to explain the immunity of epileptics to cancer (even cancer of the tongue and mouth, although the epileptic is constantly biting his scarred tongue and lips.)" Preble noted also that various affections may be arrested by pregnancy.

He then noted the fact that in the arctic regions and in the tropics cancer is rare.

In conclusion he reiterated the "singular fact that those who are practically immune to zymotic affections and germ diseases in general seem more predisposed to cancer than the average man who suffers from the contagious diseases of childhood and the same group of affections in adult life. We know little about this immunity, for as far as we can recall it has only been tested by statistics in a few cases. We do not know to what extent its origin is hereditary and familial. We do not know that it is transmissible to posterity. The evidence indicates that it is mostly individual, personal. If this immunity connotes an increased liability to cancer, then the acquired or artificial immunization of the people to zymotic disease will possibly lay them more open to cancer. It is even possible. . .that the alleged increase in cancer is the result of sanitation and preventive medicine. . .whatever it is that enables us to resist zymotic disease may weaken our resistance to cancer."

In another paper on this subject Preble (1925) stated: "There must be some connection between cancer immunity and rapid and efficient metabolism." Dercum stated (1925) that cancer rarely develops in the hyperthyroid subject. This observation was also confirmed by the Mayos, Crile, Deaver and DaCosta. Preble concluded therefore that "it is not youth that gives immunity to cancer but relatively rapid meta-

bolism." He added that this idea receives confirmation from the fact that a certain antagonism subsists between fever patients and the development of cancer. In rare cases the presence of continued fever has arrested the growth of cancer."

He pointed out that it is better to speak of a metabolic type of immunity of certain primitive races (American Indian, African negro, Polynesian, Malay, Australian black) and of various Hindus and Middle Eastern peoples, and to brethren living an ascetic life in European monasteries, Preble ascribed it to a scanty, monotonous diet, which antagonizes the development of cancer: "Both anabolism and catabolism are efficiently performed, and the metabolic type resembles that of the young, growing organism, the hyperthyroid, the hard, muscular worker, the febrile organism, the sufferer from wasting disease, the underfed and so on. Differing as these types may be in themselves, they all have essential features in common: an effective metabolism. It is conceivable that in these conditions certain deleterious waste products have no chance to form.

He re-enunciates the old doctrine of sub-oxidation as the chief factor in causing the chronic diseases of the second half of life. He suggests that cancer immunity stands in some definite relationship to super-oxidation or excess of metabolism, and that cancer predisposition is equally bound up with sub-oxidation, in a slowing of normal metabolism, in low anabolism or catabolism (the disposal of unutilized food) . . . According to the observations of Goldthwaite the habitually lean man has an abnormally lean intestine with diminished power to utilize food. This type of individual should possess some immunity to cancer, although he is often a hearty eater and eats far more than he can assimilate. (Preble, 1925)

P.F. Clark, et al (1949) discussed the effect of nutrition on resistance. Peyton Rous made one of the earliest observations on the effect of nutrition on the transmissible chicken sarcoma. He reported that concurrent illness of the host checked the development of the tumor and that young healthy well-nourished fowl proved more susceptible than the thin and the ill. Heine's original observation, that poliomyelitis seems to attack the better nourished children with relatively higher incidence

than the scrawny or ill fed, has been supported by several observers since his time. Many of these experiments show clearly and with reiterated emphasis that the typical clinical picture of several virus diseases can be markedly altered by a variety of dietary deficiencies. (Clark et al, 1949)

R.L. Smith (1957) has presented evidence which suggests that cancer and allied diseases are still comparatively rare among the Indians of the United States, who still have a higher incidence of infections and infectious diseases.

There is increasing evidence that the acute inflammatory reaction is an important factor in the host's resistance to neoplasms. Southam and Pillemer (1957) observed that the implantation of cancer cells into normal healthy volunteers elicited a marked local inflammatory reaction and rapid rejection of the transplant. In patients with advanced cancer the initial inflammatory reaction was minimal and growth of implanted cells occurred at almost all sites.

That the inflammatory reaction may trigger other resistance forces is suggested by the fact that the histamine liberated by acute inflammation appears to be a physiological activator of the reticuloendothelial system. (Jancso, 1947)

Of all the infections that are known to have caused spontaneous regressions in cancer patients, erysipelas seems to have produced the largest number of dramatic and permanent regressions. It is significant to note that an erysipelas infection in addition to the fever it invokes the toxins it produces, is accompanied by the most acute inflammatory reaction of any other type of infection.

Modern surgical technics and the use of antibiotics have made erysipelas a very rare disease in recent years, so the following early descriptions by French and English physicians may be of interest:

Deidier (1725) described erysipelas as "a superficial humoral tumor accompanied by a striking rosy color and a burning heat." Because of its redness it is called "rose", and because of its burning heat one has called it "feu sacre" (sacred fire). This malady is sometimes preceded by chills and fever, and the latter continues during the entire course. Erysipelas develops first on a small portion of the skin, and as it spreads and swells, it appears like a plateau. It moves from one area to another, leaving the part where it commenced in perfect health.

In lightly applying the finger over the erysipelatous swelling, the red color fades, only to return when the finger is removed. Sometimes in the course of the disease the cuticle is raised and forms little vesicles full of "lymphatic juice," which is absorbed as the disease runs its course. The skin then dries and scales off and new skin forms.

Erysipelas is an acute disease which ordinarily is terminated in 12 days, often happily, sometimes badly.

Deidier then spoke of "erysi-pele salulaire": - cases of delirium, pleurisy, peri-pneumonia, and other internal disorders which are cured by an attack of erysipelas. He cited the dangers of a concurrent erysipelas in pregnancy: -it may kill the fetus in a pregnant woman or cause the death of both mother and child. It is also dangerous in the newborn.

Gull (1849) discussed erysipelas as follows: "To rest satisfied with the definition that erysipelas is an inflammatory affection of the skin, would be to remain in ignorance of its practical nature. That erysipelas is of the nature of inflammation we cannot doubt: we can imitate its results by applying a blister to the skin; and when the integument is loose, we get during erysipelas, a large amount of oedematous effusion, and often the production of pus in the parts beneath, as in the eyelids. But erysipelas is a peculiar inflammation, and is not, I think, necessarily limited to the skin. . ."

Nauts (1969) in a monograph on the apparently beneficial effects of bacterial infections on host resistance to cancer, assembled 435 cases in which various types of infections developed accidentally or by inoculation. Of these 222 had microscopic confirmation of diagnosis and were followed at least five years after onset, and 106 were apparent successes, traced free from further evidence of their tumors 5 to 54 years later. Of the 116 failures 21 survived far longer than expected (i.e. from 5 to 30 years). In this study it is apparent that streptococcal (principally erysipelas) and staphylococcal infections were responsible for the largest number of successful results.

Forster (1942) made a study of the incidence of cancer among bee-keepers. He stated: "During the last few years the question has been raised repeatedly whether bee-keepers are afflicted by cancer more rarely than other people, in other words, whether the bee venom is of influence upon the incidence or upon the growth of cancer, in a similar way that it has a known curative effect in rheumatic and so-called allergic diseases (hay fever, asthma). No one has ever attempted to clear up this question in a scientific way. We first intend to create a base for the exact investigation of this problem by statistical data. For this purpose, questionnaires have been sent to all districts of Wurttemberg, Saxony and Schleswig Holstein with the request to fill them out and return them promptly. The majority of these organizations have complied with our request. We have made inquiries as to the number of bee-keepers living at the present time and suffering from cancer and of those who have died of cancer. We were interested in the age of these persons in question when they died and those who were still living and to learn which organs had been or are still affected. We also tried to find out how many years the persons in question occupied themselves with the rearing of bees, how many hives they possessed and as far as possible how many bee stings they each received. A total of 254 useful replies were received from the bee-keeper associations, of which 80 had no special remarks, 123 had short notations, and 51 had given full information. The total involved 18,623 male members and 403 female members. Seven chairmen of district groups noted the good effect of bee stings in rheumatic diseases; 23 stated that bee-keepers usually reached a good old age, and 40 chairmen, covering a combined membership of 3118 males and 75 females informed us that their observations have been made for a considerable time, in many cases extending over a period of 30 years."

Forster stated that the distribution of cancer with regard to individual organs specified in his questionnaire, agreed well with similar statistics concerning neoplastic diseases, but he noted one exception: "The small percentage of cancerous affections in the esophagus of bee-keepers is somewhat astonishing and is still unexplained."

"Our investigation showed that there are 0.36 bee-keepers afflicted with cancer for each 1,000 bee-keepers.

"In our present statistics of 0.36% in bee-keepers the average percentage is lower only in the female workers in factories and jewelry factories, showing an average of 0.3%. It should be noted that these two professions involve only young people, who as a whole, are more rarely affected by cancer than people more advanced in age. But also with regard to other trades and such with a more advanced age, the small percentage of individuals afflicted with cancer is outstanding in bee-keepers."

Forster concluded from his investigation that bee-keepers as a whole, are less affected by neoplastic diseases than other people "and that this may be due to the stings of bees, respectively, the toxin substances imparted with them." (Forster, 1942)

The following case is an example of the apparently beneficial effect of bee venom in a case of Hodgkin's disease:

DIAGNOSIS: Hodgkin's disease, confirmed by microscopic examination of the left cervical lymph nodes removed at biopsy in September 1935. Dr. Ralph Miller, pathologist of the Mary Fletcher Hospital in Burlington, Vermont, reviewed the sections in July 1937 and made a definite diagnosis of lymphoblastoma (Hodgkin's type).

PREVIOUS HISTORY: C.N.W., male, age 37 (in 1935), of South Woodstock, Vermont. The patient's maternal grandfather died of sarcoma of the leg which grew to an immense size before his death. The patient's brother died of osteogenic sarcoma in 1941, at the age of 41. A paternal aunt died of tuberculosis at 19. The patient himself weighed 12 pounds six ounces at birth, and was told that his "neck was strained during the difficult delivery." He had the usual diseases of childhood, also asthma and rheumatism, especially of the left hand. He began working in a garage in 1917, at the age of 19. He started his own shop in 1921, consisting of garage work and welding. When he was examined for Army service in the fall of 1918, he was told that he had varicose veins and high blood pressure. He was not drafted. He was married in 1921 and two children were born of this marriage, a daughter in 1923, a son in 1930.

In 1932 the patient began to keep bees as a hobby. In 1933, while taking up a wild swarm he was stung on the back and third finger. The next day the hand and forearm to the elbow were markedly swollen. Prior to onset the patient weighed 165 pounds and was 5 feet 8½ inches tall. Onset, in April 1935, he first noticed that the left cervical lymph nodes had become enlarged. Dr. A.M. Cram of Bridgewater, Vermont was consulted. On September 22, 1935 he referred the patient to Dr. Clarence F. Ball, of Rutland, Vermont, who was a cancer specialist. Ball found enlargement of the left cervical nodes, especially the deep cervicals, and a few nodes were also palpable in the axilla and iliac regions. At this time the patient was well developed and well nourished and the physical findings were otherwise negative. A blood examination showed: rbc. 5,560,000 wbc. 9,250; hemoglobin, 110; polys. 63%; S.L. 36%; eosins, 1%.

SURGERY: Ball excised one of the superficial cervical nodes for biopsy. The report of the pathologist in the State laboratory in Burlington, Vermont was indefinite. Nevertheless, Ball stated that "the clinical picture seemed definite for a lymphoblastoma of the Hodgkin's type."

CONCURRENT INFECTION: At this time the patient's children contracted impetigo and he believes he may have caught it too. He then also developed an infection of the left forefinger (sub-ungual), following a bruise; this suppurred freely. The infection lasted a month and the nail came off. It was sufficiently incapacitating so that he received workmens' compensation insurance for a time.

RADIATION: Beginning in late September 1935, x-ray therapy was administered to the left cervical and supraclavicular lymph nodes as a therapeutic and a diagnostic measure. Three treatments were given at 48 hour intervals. Ball states that "the tumors melted down to complete subsidence that was more like lymphosarcoma than that of true Hodgkin's disease if it is possible to make any such differentiation from irradiation reactions." The patient was not told the diagnosis at this time. (Possibly the unusually good response to radiation may have been due to the concurrent subungual suppurating infection.)

CLINICAL COURSE: During the next year the tumors recurred.

CHEMOTHERAPY: On July 17, 1936, Dr. Stuart Ross of Rutland, Vermont injected the varicose veins in the calves of the legs with Sodium Morrhuate 5% W Benzyl alcohol 2%. For several months the patient wore bandages on the legs.

FURTHER RADIATION: During September 1936 three more x-ray treatments were given for the recurrent enlargements of the cervical lymph nodes again resulting in complete subsidence: no palpable nodes remained.

CLINICAL COURSE: On February 3, 1937 the patient again came to consult Ball because of further enlargements "not only of the left cervical but also of the right, both axillae and both inguinal regions. The generalized external glandular enlargements and the general condition indicated a constitutional reaction that had not appeared formerly upon examination. A loss of weight and a considerable loss of working ability were especially noted."

FURTHER RADIATION: At this time Ball administered x-ray therapy to all the affected areas, "including the epigastric region, inasmuch as there seemed to be palpable tumor about the celiac axis." A course of 12 treatments were given in four weeks. Again there was complete regression.

CLINICAL COURSE: The patient came back for a check-up a month later that was satisfactory. On April 28, 1937 there was still no evidence of further lymphadenopathy, but Ball stated that he showed "a definite wasting away in body contour from the robust appearance he made at the first examination." At this time the patient became suspicious that his condition was malignant, and finally succeeded in getting Ball to tell him the diagnosis. Hoping that a mistake had been made, he went to the Hitchcock Clinic in Hanover, New Hampshire. On July 8, 1937, Dr. M. Dawson Tyson removed a small node from the supraclavicular region. (This area had recently received x-ray therapy.) The specimen was reported as showing "fibrous connective tissue. No lymphoid tissue. No evidence of tuberculosis or malignancy."

The clinical history and the sections from the original biopsy by Ball were then

reviewed by Dr. Nathan T. Milliken of Burlington, Vermont, who reported to Ball on July 19, 1937: "After receiving your (clinical report) and reviewing the slides which you kindly forwarded, we entirely agree with your diagnosis. . . Dr. Ralph Miller, our pathologist, feels that he can make a definite diagnosis of lymphoblastoma (Hodgkin's type) from the slides."

FINAL COURSE OF RADIATION: A fourth and final course of x-ray therapy was given by Ball in April 1938, lasting four weeks. The right axilla, right groin, spleen and the hilus of the left lung were treated. (Chest films taken the previous year had indicated involvement in that area.) The patient became very nauseated following some of these treatments.

CHIROPRACTIC THERAPY: In May 1938 the patient "became convinced that he was going to die anyway and so decided to save what money he had left for his family" and therefore declined further x-ray therapy. At this time his weight had decreased 15 pounds to 150 pounds. In July 1938 he was persuaded by a neighbor who was a student at Dr. B.J. Palmer's Chiropractic School in Davenport, Iowa, to go out to Palmer's Private Clinic. He stated that they "found a rotated condition on one side between the atlas and axis bones in my neck. Palmer personally gave me the only chiropractic adjustment I have ever had - quite a shock, I stayed in Davenport a couple of weeks and was checked daily with their neurocalograph." Further x-ray films were taken following this form of treatment which were reported as "showing the bones in correct position." Palmer advised the patient to discontinue all heavy neck-straining work connected with his garage, and he did so, allowing his assistant to do the heavy jobs.

BEE VENOM AND HONEY: He returned to his home in Vermont in July 1938. He stated: "At this time I expected my days were to be short, and to keep my mind off my prospects I put in a lot of time with my bees, which resulted in my getting plenty of stings." (During that period he sometimes was stung 25 to 75 times a day, but later he averaged only three or so daily. At this time he also bought honey for resale, and he began eating much more of the extracted honey than he had of the

comb honey he had formerly raised himself. (Later he produced his own extracted honey.) During the next few months, that is, the latter half of 1938, the tumors decreased markedly in their growth rate, then decreased in size. In November 1938 the patient reported to Ball by letter that he was apparently getting along well, that he had not discovered any new tumor masses and that he felt "all right; the best I have for some time. Am not bothered with any cough." By January 1939 the nodes were a quarter their former size, and they gradually regressed until they were no longer palpable.

CLINICAL COURSE: There has been no further recurrence of the Hodgkin's disease since the patient recovered in 1938-1939. He has continued to lead an active life, maintaining his garage and machine shop in addition to the bee-keeping, and being selectman of his town in recent years. He stated in 1955 that formerly he had been very sensitive to bee stings, but that gradually he became immune unless stung in the nostril or near the eyes. In March 1949 Dr. O.S. Peterson, radiologist at the Mary Fletcher Hospital in Burlington, wrote to Ball (who had not heard from the patient for a decade) stating that the patient was free from disease. At this time Ball replied: "We had not really expected Mr. W. would still be about . . ." The patient's weight increased from 150 pounds in 1935, prior to onset, to 180 pounds in 1955. He stated that there was never any evidence of lymphadenopathy or other symptoms after 1939. His only problem was psoriasis and varicose ulcers for which he was treated by his family physician. He was last traced in excellent health January 1970, 35 years after onset. (New York Cancer Research Institute Records)

COMMENT: In evaluating the successful outcome in this case, one should attribute the result to no single factor, but rather to the combination of small doses of radiation, the concurrent infections, and the bee venom (of which he had so much during the period in which the final complete regression and control of the disease occurred). One should also perhaps consider the possible stress produced by the shock of the chiropractic "adjustment" which may have had some adreno-corticomimetic effect. (New York Cancer Research Institute Records).

In the 19th century inflammation was induced by citric acid, acetic acid, chloride of zinc, silver nitrate, iodine, iron, creosote, turpentine, zylol and various caustics or vesicants. These were used in Europe between 1856 and 1900. Other physicians used cupping or fixation abscesses in an attempt to evoke the beneficial effects of inflammation in cancer patients. Their experiences are briefly reviewed as follows:

In 1856-57 Simpson first suggested injections of a few drops of sulphate or chloride of zinc, iron, creosote, etc. with an acupuncture needle into, around, or beneath the tumor to "destroy its vitality." The tumor itself was thus "Subsequently thrown off by the process of spontaneous enucleation. The needle is thus substituted for the knife and the operation is quite bloodless." (Cited in Med. Times & Gaz. 2: 483, 1866)

Broadbent (1866) used large quantities of dilute acetic acid, injected into malignant tumors. Mr. C.H. Moore spoke very highly of Broadbent's method on three recurrent neoplasms all of which disappeared entirely. He cautioned physicians using this method not to attempt to cause necrosis of large tumors all at once because "the amount of debris might be too large for absorption. . . ." He warned that when the skin is involved, or when the tumor is of large size or rapid growth, one cannot expect absorption, but one may be able to cause it to be destroyed and discharged by sloughing. In such cases he suggested a different technic: the injections should be most thorough, and the acid strong, so that the entire disease may be removed at once. . . . It is possible, perhaps probable, that there will be less liability to local return of the disease after removal of a tumor by acetic acid than by the knife, as the acid being more or less diffused in the surrounding tissues may reach germs which would have escaped the knife; and there is more reason to hope that such will be the case from the excellent results which have followed the application of chloride of zinc after cutting operations as recommended by Mr. de Morgan. Broadbent then described four cases treated in this way of which the following was reported in detail:

Female adult; twice recurrent inoperable mammary carcinoma; onset 1864; mastectomy; recurrence; second operation, August 1865; second inoperable recurrence May 1866 of even more rapid, overlying skin adherent; May 18 and 23, 1866: 30 minims dilute acetic acid injected into egg-sized recurrence, little or no pain, further injections June 7 and 9 of somewhat stronger acid caused pain, swelling, free drainage and marked decrease in size, no further improvement until cavity was dressed daily with strong acetic acid and injections were also given daily. "This energetic treatment gave much pain, and excited inflammation all around. There was also considerable hemorrhage. . . as a result of this acute inflammatory reaction the remains of the neoplasm were entirely destroyed, leaving a healthy granulative surface." ^{end} result unknown. (Broadbent, 1866, p.229)

In the discussion of Broadbent's paper Hey noted that "the constant application of tincture of iodine. . . so as to penetrate the surface. . . has been known to keep patients alive for three or four years. Iodine 'blistered the surface of the tumors.'" (Broadbent, 1866)

Others such as Brandini in Florence or J.F. Clark (1866) in England observed that citric acid assuaged the violent pains of cancer patients. Brandini cited a case of a male, 71 with inoperable cancer of the tongue involving the base, the sublingual and submaxillary lymph nodes. "The patient asked for a lemon which is nothing remarkable as cancerous patients generally have an extraordinary liking for acids. . . the juice of the lemon diminished the pain. The following day he asked for another. This gave him greater relief than the day before." This led Brandini to use citric acid in a crystalized state as a gargle: (4 grams in 350 grams of water) with complete pain relief. In the course of a month there was not only complete cessation of pain but the swelling of the tongue reduced very considerably.

Moore (1866) discussed Broadbent's method as follows: "It is strangely novel, inasmuch as it chemically dissolves the cancerous cell in the midst of the tissues; and it is strangely successful, for it has effected the absolute dispersion of small cancerous tumors, without destroying, as caustics do, the natural textures in which the tumours lay."

" . . . Acetic acid dissolves cancerous tumors, and the absorbents may remove the inert remnants of it; but the acid does not change the disseminating power of the disease. If fragments be left beyond the limits of a tumor, they will grow again, whether the main mass has been cut away with a knife or dissolved away with acid."

He warned against using too strong a solution, which would then act as a caustic, producing slough. Barclay claims to have originated the use of acetic acid on cancer. He used citric, acetic, and carbolic acids, but he used them superficially on ulcerated cancers.

Moore describes his use of injections of chloride of zinc or sulphate of iron on two or three cases: these were very painful to the patient and produced local necrosis and sloughing with rather inconclusive results. (Moore, 1866, 1867)

Professor Karl Thiersch of Germany attempted to find a substance that could be injected into tumors which would remain in contact with the neoplastic tissue for a long time, and which would cause as little lixiviation as possible. His objective was not merely to kill the tumor cells directly, but to exert an anaplastic effect on the tumor bed.

The first substance he tried was iodine, but this was too easily absorbed and disappeared from the tumor too rapidly: injections had to be repeated so often that this caused mechanical irritation in the tumor (swelling). He therefore rejected iodine and also arsenic because it can have a dangerously toxic effect on the entire organism. He also tried phosphorous. He finally chose silver nitrate in very small doses (in his first case 1:5000, later 1:2000). Nussbaum also used this method in doses of 1:2000 followed by injections of sodium chloride. Of the 15 skin cancers so treated, four disappeared after the patients developed suppuration and gangrene, in six the result was moderate and in the other five it was slight. (Nussbaum also injected pepsin and acetic acid in some cases). Nussbaum believed that it was essential to saturate all portions of the neoplastic tissue with the injected material. Völker used injections of silver nitrate in much larger doses than recommended by Thiersch: on a tumor the size of a fist 0.5 grain was used and then 6/19 of a grain of actual

silver. Although Völker did not consider Thiersch's method good, he could not deny that absorption and discharge of tumor tissue with pus did occur, but not in every case. Thiersch attributed success to the dynamic effect of the silver, but Völker did not believe this was proved.

Völker believed that the acute artificial edema should be regarded as the most important factor. Microscopic examination of the tissue showed cells which had swelled through endosmosis before rupturing. Following this the growth of the carcinoma ceased and the odor due to ulceration also ceased. The artificial edema of the tumor increased to a much greater extent than the surrounding tissues at first, and later the injected fluids passed into the surrounding tissues, which speeded the resorption of the tumor.

Two cases treated by Völker were given injections of water, causing local inflammation, swelling, reddening, pain, discharge of pus, and finally necrosis of the inflamed tissue. Sometimes there was no local reaction at all, but this did not surprise Völker, who believed that one patient might be much more sensitive than another to such treatment. (The water was probably contaminated with bacteria in some cases but not in others.)

It is of interest that in both the cases Völker observed in the Greifswald Clinic given silver and saline injections, erysipelas infections developed, followed by regression and pain relief in one case and complete disappearance of the extensive tumor mass in the other. (See below for an abstract of the second case.) Völker, Nussbaum and Thiersch did not attribute any beneficial effect to these concurrent erysipelas infections, having apparently been unaware of the case published by Busch (1866). Most of the many other cases suggesting the salutary effects of concurrent erysipelas were reported in the period from 1882 to 1900.

The following history is that of Völker's second case:

Male, 49; extensive inoperable carcinoma inguinal region; onset, about June 1866; physician consulted when larger growth was size of ^aman's fist, 2 smaller ones size of a child's fist. Hot, wet dressings were applied in the hope that the condition was an abscess; larger tumor excised causing severe hemorrhage and pain; evil smelling dis-

charge from malignant ulcer ensued, indurated carcinomatous masses infiltrated surrounding tissues toward thigh to spine of ilium (13 x 14 cm.), extending deeply into peritoneum; June 1867: 7 ampoules of silver salts, 5 ampoules of saline injected, causing severe pain, edema, surrounding skin tense and red, febrile (38.2°C), pulse 74; tumor increased in volume due to edema; next day pain increased, skin intensely blue-red; profuse discharge; erysipelas developed that day, marked suppuration fever (40.2°C); 7 days after erysipelas developed, cough, dyspnea, pneumonia; general condition failed rapidly, but bottom of carcinomatous ulcer "completely cleaned out, entire great tumor mass had disappeared without leaving a trace"; death 4 days after pneumonia set in. (Völker, 1867; Meyer, 1931, pp. 343, 367-368)

In concluding his thesis Völker ascribed the success of the two Greifswald cases to Thiersch's silver and saline injections, stating that in favorable cases those injections can discharge neoplasms by sloughing, not by absorption, and that in any case they remove the foul odor. He admitted that the treatment was painful, but believed it was indicated in some cases. (Völker, 1867)

It is significant to observe that in a number of the early recorded cases in which acute erysipelas injections developed spontaneously, some form of irritating local treatment was administered prior to onset of the erysipelas: Lussana and Tansini (1868) applied gastric juice; Mosengeil (1869), actual cautery; Mishtolt (1883), chloride of zinc injections; Wyeth (1884), Fowler's solution injections; Verneuil (1886), "an irritating ointment"; Senger (1890), methyl violet; Pacinotti (1898), silver nitrate.

In addition to all these cases in which some form of chemical inflammation or irritation occurred there were a considerable number in which a biopsy or exploratory incision was made, thus also producing a certain amount of inflammation in the tumor and (especially prior to 1900), making it easier for an infection to develop locally.

COMMENT: These observations suggest that in treating patients with bacterial toxin therapy now and in the future, a few of the injections should be made in various portions of the tumor or its immediate periphery (wherever accessible), in order to set up an inflammatory reaction which will help concentrate in the tumor area the defensive substances activated systemically by injections given by other routes remote from the tumor.

Schöbl (1896) reported a case of retinoblastoma with concurrent acute inflammation in a female, aged three. There was spontaneous regression following acute and the use of "irritating" medication by a quack. The child suddenly died of diphtheria three months later just as the tumor appeared to be recurring. At post mortem examination of the affected eye revealed that the bulbus appeared to be still smaller, the sclera still thicker, the conjunctiva normal, the anterior chamber a little flatter. The pupil and the iris were full of round and spindle cells and liquid debris. The back part of the eye was filled with a similar substance. In the lens there appeared cavities in which there were myelin globules and bits of detritus. Behind the lens lay an extensive layer of inflammatory tissue from the ciliary body consisting of round and spindle cells, the intermediate substance and some neoplastic blood vessels. The whole vitreous body was full of necrotic products of regressing tumor elements, which did not take the hematoxylin stain. The optic nerve appeared to be infiltrated. Extending from it to the tissue surrounding the pupil, there was a funnel-shaped mass of glioma cells which infiltrated into the vitreous body which was filled with necrotic tumor tissue. The choroid appeared to be very much involved from the pupil to the ciliary body. There was a clearcut line of demarcation between the necrotic products of the older portions of the tumor in the vitreous body and the actively growing retinoblastomatous masses of the choroid.

Schöbl regarded these findings as indicating that the primary tumor which he had originally diagnosed with certainty as "glioma retinae endophytum," had gradually grown into the vitreous body until it filled it completely. In the meantime the growth also infiltrated the optic nerve and the choroid. An acute iridocyclitis then developed, which, through the "senseless" treatment of the quack (irritating medicines) became more acutely inflamed. The primary tumor then began to regress, influenced by this intense inflammation. The whole tumor filling the vitreous body also began to regress and progressive atrophy of the bulbus could be seen. Later the recurrent tumor started to infiltrate both the opticus and the choroid, and this caused the enlargement of the bulbus and increased intra-ocular tension, apparent just prior to the diphtheria infection. Schöbl did not attribute any of the regression to the concurrent diphtheria. (Schöbl, 1869)

Luton (1874) believed that the physician's role was not terminated after surgical removal of cancer, for one always fears recurrence, a fear which is too often justified, the most frequent site being the regional lymph nodes. Even in the most favorable circumstances one is never certain that one has not neglected some already diseased node. Also the operator may hesitate to explore too deeply in such regions as the axillary vessels.

Nevertheless, if one had a simple and practical means of preventing these further accidents, one would not omit using it in many cases, to give security both to the patient and the physician.

Luton believed we possess such a method, and he described it thus: It consists of introducing by injections either in the enlarged lymph nodes or in the interstitial cellular tissue surrounding the former tumor area, a more or less destructive or neutralizing liquid. In two cases which he then described, he used tincture of iodine in one and chloride of zinc in the other. Both recovered and remained free from recurrence or further metastases when last traced, one 11 years and one 14 months after treatment. The second case, a breast cancer (1872) developed a wandering post-operative erysipelas infection and received one injection of chloride of zinc in an enlarged axillary lymph node which was considered to be metastatic - causing complete regression. The patient remained entirely well over a year later. The other, a cauliflower growth at the base of the tongue, with a submaxillary lymph node metastasis received two injections of pure tincture of iodine in the node and caustics to the primary growth. This patient was traced well 11 years. (Luton, 1874)

Pozzi (1878) described in detail a case of a female aged 25 with bilateral malignant ovarian papilloma ("epithelioma myxoides") with ascites (10-12 litres of fluid removed each time) He therefore injected 100 grams of tincture of iodine intraperitoneally, causing intense pain, fever, and distention lasting 36 hours, i.e. induced peritonitis. The ascites rapidly returned, but was less abundant. A third paracentesis yielded 13 litres. At this time 150 grams of tincture of iodine were injected intraperitoneally followed by a violent peritonitis lasting 15 days. Three weeks later the abdomen was as large as it had been prior to the third paracentesis. A quack then treated her with repeated purgatives, followed by notable diminution of the ascites for eight months. A fourth paracentesis on March 2, 1878 yielded 16 litres. Ascites did not recur for seven weeks and at the fifth paracentesis 15 litres were withdrawn. In late August, 1878 she consulted Pozzi in Paris, as her abdomen was the size of a full-term pregnancy and she insisted upon an operation. A final paracentesis yielded 14 litres of fluid containing rather numerous leukocytes and other edematous lymphatic cells, a great deal of mucin, a few erythrocytes, and not a single cancer cell. Pozzi and Terrier operated in September 26, 1878, assisted by four other surgeons. They found marked vascularity of the abdominal walls, requiring the application of numerous hemostats. On opening the peritoneal cavity, a large quantity of ascitic fluid was evacuated and a cauliflower mass, the size of a full-term fetal head was found in the left flank which filled the entire pelvis and extended up to the hypogastric region. It appeared to be made up of innumerable small cysts which were agglomerated into one mass. It was attached to the broad ligament and to the uterus which it encased. The original 8 cm. incision was enlarged another 4 cm. to the umbilicus. The polycystic mass was separated and removed with great difficulty, leaving two pedicles which were much too short. The pelvis was then cleaned carefully, as it had been covered with blood and much debris from the tumor, which had broken into fragments, having the aspect of hydatid cysts. It was then noted that the abdominal cavity had a very unusual appearance: the parietal peritoneum was wine-red in color, indicating an increased vascularity, as was noted in the abdominal walls. The intes-

tines were matted together in one voluminous mass by adhesions. These two factors (increased vascularization and adhesions) were deemed a result of the two injections of tincture of iodine, followed by induced peritonitis which the patient had experienced. The large space formerly occupied by the tumor, especially the recto-vaginal cul-de-sac, was gaping extensively, and Pozzi decided to leave a drainage tube in this empty space, because he was sure it would become filled with sero-sanguinous fluid.

The first two days after operation the patient had a rather high fever: 39.5°C . There was abundant sero-sanguinous drainage from the drain. Lavages of the vagina and the wound via the drainage tube were done with dilute alcohol and phenol. The third day the temperature was 38.2°C . The general condition seemed better and the abdomen was no longer painful on pressure. Suppuration appeared in the drain and in the vagina. The temperature spiked daily until the 16th post-operative day (38.5°C . to 39.8°C .). By October 10, 1878, suppuration had almost ceased. The patient had to be catheterized for the first 16 days after operation. Thereafter this was unnecessary, and although she continued to have a slight fever, convalescence began. On October 18th, 19th, and 20th, there was some retention of pus in the wound and on October 20th, two large spoonfuls of pus drained from the suprapubic sinus. The sinus was probed and found to be 20 cm. in depth. On October 22, 1878, a small abscess broke open spontaneously in the lower part of the cicatrix, 2 cm. above the insertion of the drain. About two spoonfuls of pus drained out. From this time on there was steady and rapid improvement. The sinuses where the drain and the abscess had been, closed promptly. The patient returned to her home in the country the end of November, two months after operation. She made a complete recovery and remained well 20 years, to the middle of 1898. Ascites then again appeared. The abdomen enlarged considerably, with edema of both legs, due to compression.

A second operation was performed on December 10, 1899. The recurrent tumor was quite fixed to the pelvic floor, and as the patient was in very bad condition, Pozzi did not attempt to remove it, but merely drained it.

The patient made a rapid though temporary recovery. The ascites and the edema

of the legs disappeared, and her health was again satisfactory for about one year. Death occurred on May 4, 1901, 25 years after onset.

Pozzi (1904) stated that this case presented the longest survival of any of his ovarian cases, and added: "I am not aware of any other example of relapse after such a long recovery. If this patient had died two years sooner, she could have been quoted as an example of permanent cure; in fact she was so mentioned in the second edition of my Treatise on Gynecology, 1897." (Pozzi, 1904)

Thornton (1881), an English gynecologist, in reporting his end-results in a surgical treatment of ovarian tumors, stated that following removal of malignant ovarian tumors, in which extensive peritoneal implants were left, these "may disappear either with the removal of the tumor. . .or possibly by the irritation (inflammatory reaction) induced by the sponging, etc., at the time of operation." (Cited by Taylor and Alsop, 1932)

SPONTANEOUS REGRESSION OF PERITONEAL IMPLANTATIONS FROM OVARIAN PAPILLARY CYST-ADENOMA:

"The disappearance of the secondary peritoneal implantations after the removal of a primary ovarian growth is a phenomenon accepted by most gynecologists, but treated with some scepticism by one or two of the special students of ovarian tumors. Very few instances of this apparently spontaneous regression have been reported in recent years, and the earlier cases are incompletely described...." (Taylor and Alsop, 1932, p. 1305)

The distinguishing clinical features of these cases with benign implants are the gradual development and slow progress of the disease, the marked ascites, and the patient's youth. The onset is usually insidious, but occasionally the abdominal enlargement may follow closely upon an attack of acute pain, which many of the earlier writers interpret as indicative of rupture and dissemination of intracystic vegetations. Loss of weight and strength are common symptoms and patients may live for long periods in a state of marked cachexia. Ascites is the rule, the fluid being sometimes clear, sometimes sanguineous, and hydrothorax has been reported in cases that have eventually made a complete recovery. Many of the patients are tapped repeatedly be-

fore their first operation, and not a few have undergone a simple celiotomy before the definitive operation for removal of the primary tumor has been undertaken. When ascites is found complicating a slowly progressing ovarian tumor in a young woman, a benign papillary cyst-adenoma with peritoneal implants may be suspected, but such a favorable type of growth is extremely rare in women over 50.

The role of the celiotomy in promoting the disappearance of the implants is not clear... .It has been suggested (Fraenkel) that an inflammatory reaction of the peritoneum to its exposure causes a stimulation of connective tissue activity which destroys the implants. A far more plausible explanation (in Taylor and Alsop's opinion) was that absorption of the implants is a continuous process, taking place with equal speed before the operation, and that the function of the celiotomy, either by removal of the tumor or the ascitic fluid, is but the elimination of the source or the means of transport of the necessary supply of new implants.

Tait, Professor of Gynecology in Queens College, Birmingham, England stated: "I have had more than one occasion to draw attention to the astonishing disappearance of tumors often of large size, after a mere exploratory incision. The cases in which I have seen tumors disappear have been mainly cases of diseases of the liver, spleen and head of the pancreas. I have seen others where the exact site of origin could not be accurately ascertained, disappear equally and I have also seen at least one case of uterine myoma go away after simple exploratory incision. The cases are far too numerous, and the results indicate sequence far too clearly for us to dismiss the phenomena as a mere coincidence... .I am satisfied that the mere opening of the peritoneal cavity has a direct influence on setting up the process of absorption of the tumor. . .that some emphatic physiological change is at once set up by opening the peritoneal cavity is clearly indicated by the uniform onset of a most distressing thirst, which lasts for days, and is not so marked after any other operation known to me. Let the incision in the abdominal wall be made down to the peritoneum but let the serous cavity remain unopened, and this thirst is not marked, but let the peritoneum be opened a fingers breadth and the result is remarked." (Tait, 1889)

In the discussion which followed the report of a case of inoperable spindle cell sarcoma of the parotid successfully treated with Coley's toxins, at the New York Academy of Medicine, January 8, 1900, at which the patient was presented for observation, Dr. John A. Wyeth asked: "What was the object of introducing the toxins directly into the substance of the tumor, and was it Dr. Coley's custom to do this?"

Coley replied that it was his practice whenever it was feasible, his experience having been that the results were far more satisfactory and more rapid when this could be done. He had, however, had good results in several cases in which it had been necessary to make the injection at some distance from the growth.

Wyeth asked if the temperature and inflammation had been exaggerated by this direct injection method.

Coley said that he thought this was apt to be the case, especially if sloughing were present, but that pyogenic infection could be largely avoided by careful cleaning and disinfection before making the injections.

Wyeth said that he had asked these questions because his own experience had led him to believe that much of the beneficial results following the injections of Coley toxins was due to an inflammatory process not directly connected with any special virtue of these toxins. This statement was not intended as any criticism of the toxins, because he believed they were directly beneficial and that Coley's method was both scientific and successful.

He cited his own two cases of sarcoma of the abdominal wall in which acute inflammation and suppuration occurred followed by complete regression. He believed "it was essential to secure infection with the erysipelas coccus" to secure satisfactory results. (Wyeth, 1900) These cases were abstracted in full and included in the monograph (Nauts, 1969) ^{are}

Wyeth then cited a case of sarcoma of the abdomen who developed "great inflammation" immediately after an exploration by Barton in 1897. The growth which was inoperable, regressed completely in six weeks and the patient remained in good health when last traced four years later (Wyeth, 1901, p. 596)

Among the physicians who used turpentine injections to induce an inflammatory reaction were Krynski, Kronacher and Goodale, whose experiences are briefly cited here:

Having observed a complete temporary regression of a malignant goitre following a severe wound infection, Krynski (1895) resolved to ascertain whether or not suppurative changes of an aseptic character, with complete absence of danger, would favorably influence the growth of malignant tumors when artificially produced.

In two advanced cases of carcinoma of the breast, he injected oil of turpentine in order to induce "artificial suppuration." No result was obtained, save the infliction of considerable suffering on the patients. Although necrotic tissue was thrown off from the diseased area when suppuration was well established, the tumor continued to infiltrate the neighboring structures, with pain. The end result was not recorded in these cases.

The good results following inoculations of erysipelas encouraged Kronacher (1895) to try turpentine injections. He stated that he obtained "very remarkable changes in a carcinoma by this means."

The only detailed history was reported by Goodale (1908):

DIAGNOSIS: Inoperable lymphosarcoma of the tonsil, confirmed by microscopic examination by Dr. J.H. Wright, pathologist of the Massachusetts General Hospital, Boston, Massachusetts.

PREVIOUS HISTORY: Female, age 35, of West Roxbury, Mass. The patient gave a history of having had pain in the left tonsil and adenitis several weeks previously. The condition at that time suggested a severe type of diphtheria of one tonsil, with swelling and exudate. The patient first consulted Dr. J.L. Goodale on April 15, 1907, at which time the left tonsil was transformed into a firm reddened mass about the size of a hickory nut with deep extensive ulceration. The lymph nodes on that side below the angle of the jaw were enlarged, firm and slightly tender. Examination of the blood was negative. The clinical diagnosis was sarcoma. A portion of the growth was removed and reported to be lymphosarcoma of a rapidly proliferating type. The growth rapidly increased in size and the cervical nodes became very much enlarged. By May 4, 1907, the patient was breathing with difficulty. She was examined under ether with the object of removing the growth if possible. However, since it was extensive, having infiltrated the soft palate, and the base of the tongue, no surgical procedure was attempted.

INDUCED INFLAMMATION COMBINED WITH TOXIN THERAPY: Because Goodale had observed a spontaneous regression in a case of Hodgkin's disease two months before, following a series of furuncles he decided to attempt to produce suppuration by injections of turpentine. These were made in the legs. Two minims were injected on May 25 and 27, 1907, without results, except that the sites of injection became rather red and painful. At the same time injections of Staphylococcus aureus vaccine were given every three days. The dose of turpentine was increased every two days to a maximum of 12 minims. Within one week the patient began to show improvement: swallowing was easier, so that she could again take solid food. The general condition was also better. By June 8, 1907, she was able to go outdoors and two days later was talking easily, the growth in the throat having steadily decreased in size. By the middle of June, it had nearly disappeared. The turpentine injections which up to that time had been borne without

great discomfort, became very painful, and on June 14, 1907, she began to have localized necrosis of the skin from these injections. On June 29, 1907, she returned home.

CLINICAL COURSE: By July 10, 1907, the site of the growth in the tonsil was a large stellate cicatrix, with absolutely no trace of tumor remaining. The infiltration in the tongue and soft palate had also disappeared and the cervical lymph nodes had become so small that only one was palpable about the size of a hickory nut. The patient was again examined by Goodale in September 1907 by which time the cervical nodes had entirely disappeared. The patient later married. She remained in perfect health and free from recurrence when last traced in November 1913, over six years after onset.

COMMENT: This case is of interest since it is known that staphylococcus toxins alone may have little or no effect on neoplasms. The combination of inflammatory exudates and these toxins appeared to be very effective. Tanchou (1844) cited cases in which a seton was induced in cases of cancer on one or more limbs, and which produced complete regression of the neoplasms. (Goodale, 1908; W.B. Coley's office records)

While the following case seems to be "spontaneous", it is of interest to note that turpentine and sulphur were administered just prior to the regression.

DIAGNOSIS: Malignant melanoma, primary on the anterior chest wall, with multiple metastases, confirmed by microscopic examination.

PREVIOUS HISTORY: H.S., male, age 38, a stockbroker. The family and early personal history are not recorded. The patient had a congenital mole on the front of his chest. This began to enlarge in June 1902.

SURGERY: It was excised in October 1902. A small healthy scar marked the site of the operation. Shortly after the operation tiny dark blue or black nodules appeared in and under the skin, being most numerous on the front of the trunk. The patient then began to drink whisky very freely and he took arsenic for some weeks. On June 23, 1903 he consulted Mr. A. Pearce Gould, F.R.C.S. Examination at this time revealed several coal black spots the size of mustard seeds or lentils almost all of which were felt as little nodules in the skin. One or two were impalpable. They were firm and quite painless. There were two nodules on the right groin, one on the left, but none on the lower extremities. The lymph nodes were distinctly enlarged in each groin, in each axilla and in the right posterior triangle. The urine was a deep purplish black containing melanin. The liver was felt below the costal margin.

MEDICATION: Pearce Gould discontinued the whisky and arsenic and prescribed a pill of Venice turpentine and flowers of sulphur. Within three weeks, by July 14, 1903, there was remarkable improvement in the general condition. No new nodules had appeared and all the old ones were flatter and smaller. The enlarged lymph nodes were also smaller. By July 30, 1903, many of the nodules had disappeared altogether. Others were present as black stains, visible but not palpable. The lymph nodes had further diminished in size. By October 1, 1903 he had gained weight and appeared to be in robust health, working regularly with no fatigue. Only one palpable nodule was present over the entire body, although there remained three black stains on the face and six on the body. The lymph nodes in the groin were normal, those in the axillae slightly enlarged, but only a quarter of their former size. The liver could not be

felt below the ribs. On December 1, 1903 the general condition continued to be very good. The nodule in the left groin had disappeared. One black stain remained on the right abdominal wall and one over the right scapula could just be palpated. The others were impalpable. For six months there was marked and continuous improvement in the local and general condition, the stains of deep black melanin were absorbed although the melanuria continued.

CLINICAL COURSE: On February 1, 1904 the patient seemed very well but a new black nodule had appeared over the upper inner aspect of the knee. (The first to develop in the lower extremities.) The patient had lost four pounds in recent weeks. Three weeks later another tiny nodule appeared in this region and pain was felt over the right lower ribs, due apparently to a tongue-like enlargement of the liver. During March the liver continued to enlarge and a fresh nodule appeared on the right side of the neck. The patient died in September 1904, having been confined to bed only three or four days, although for nine weeks he suffered from hallucinations.

In reporting this case Pearce Gould stated: "I do not record this interesting case as an example of the therapeutic value of Venice turpentine and sulphur in this disease, but of the infinitely more important and pregnant fact that there are physiological forces which are able not only to stop the spread of secondary growths of melanotic sarcoma, but even to destroy such growths when they have formed. The existence of these natural powers is the justification for the confident hope that malignant disease is curable, and it is the knowledge of them and of their conditions that will probably solve the problem of the prevention and cure of cancer." (Pearce Gould, 1903; cited by Handley, 1907.)

In the following case hypermia was induced by cupping:

DIAGNOSIS: Extensive inoperable small celled sarcoma of the left shoulder with supra-clavicular lymph node involvement, confirmed by microscopic examination following biopsy by the Pathological Institute at Griefswald, Germany.

PREVIOUS HISTORY: Male, age 20, mason, of Posen, Germany. Onset, in the autumn of 1904, a tumor was first noticed in the left neck and shoulder region. In spite of various medications the disease progressed and by 1906, the patient could no longer raise his left arm. He was admitted to the City Hospital in Posen early in April 1907. Examination revealed a big, strong, well-nourished young man. The left shoulder was the site of a huge tumor extending over the middle of the scapula to within three finger breadths of the cervical vertebra posteriorly along the left arm nearly to the insertion of the deltoid muscle and anteriorly to the coracoid process. The overlying skin was bluish-red with many enlarged veins and was completely immovable. The tumor was soft, almost spongy although in some areas it was more resistant, the latter areas being painless. There was passive mobility of the shoulder joint, but the left arm could be moved only a little above the horizontal position, and there was considerable muscle atrophy. The supraclavicular fossa was almost completely filled with soft tumor tissue, apparently originating in the lymph nodes. This tumor mass was rather precisely demarcated and was movable over the underlying tissues. There was no other lymphadenopathy. The preoperative diagnosis was inoperable sarcoma, but to confirm the diagnosis, Dr. C. Ritter decided to attempt to remove the tumor from the supra-clavicular fossa for microscopic examination.

SURGERY: This was done on April 6, 1907, under Schleich's infiltration anesthesia. The operation did not prove to be as easy as Ritter expected. Upon incising the skin, a very large varix appeared overlying the tumor mass. These vessels were readily ligated, but upon further attempts to extirpate the mass in toto, it seemed quite inoperable. It was not only extremely vascular, but in spite of its being movable, it had infiltrated the surrounding structures in all directions. The attempted removal, therefore, had to be abandoned and Ritter only removed a larger portion of the tumor

than would have been done by simple biopsy. At once a profuse hemorrhage occurred from the incised portions of the supraclavicular mass. Ligatures and purse-string sutures only partially succeeded in arresting the bleeding. Many clamps were required and the whole bleeding area was packed with tampons, over which the skin was sewed and the incision closed. A compression bandage was applied and a saline infusion was given. The patient recovered from the loss of blood on the day after the operation. On the second post-operative day the tampons were loosened and on the fourth day they were removed. On the eighth post-operative day there was good granulation, little secretion, and healing appeared to be progressing well.

ARTIFICIAL HYPEREMIA: In the hope of influencing the main mass of this huge inoperable sarcoma, Ritter began applying glass suction cups daily to the tumor area six days after the exploratory operation. Ritter stated: "To our great astonishment, by April 29, 1907 (17 days) the whole tumor seemed to have diminished so that the normal shoulder line could be distinguished. The cavity which had been packed with gauze tampons was healed except for one small area." The huge primary tumor and supraclavicular involvement entirely disappeared. The patient made a complete recovery and was discharged from the hospital as cured on May 12, 1907, one month after Ritter had begun treatment. At this time the affected shoulder appeared normal, except for a thick scar at the site of the exploratory operation.

CLINICAL COURSE: The patient was instructed to return immediately if there was any evidence of recurrence. He was not heard from again until May 6, 1917 (13 years after onset), when he wrote to Ritter and stated that he had remained in good health after his discharge from the hospital 10 years previously, and had been able to return to his work as a mason. He was drafted into the German Army on June 1, 1915, fought in the infantry against Russia, and later in France. In May 1917, he was admitted to an Army Hospital from the battlefield because of "pains in the stomach and neuralgia of the left arm." His military surgeon, Dr. Runze, reported to Ritter at this time that the patient's gastric complaints seemed to be due to defective dentures. He stated that the patient also had had some neuralgia in the left arm (the affected arm)

and this was attributed to the hardships and exhaustion of army life and to the cold climate. In the region of the exploratory operation there was a perfectly normal scar. The posterior portion of the deltoid muscle was atrophied. There was slight atrophy of the whole left arm, and analgesia of the supra-spinatus fossa. The left arm tired more easily when working, causing neuralgic pain radiating down to the hand. Motion of the shoulder joint was very good. There was no evidence of recurrence. X-ray examinations of the shoulder joint and of the inner organs were negative. Runze added that the patient was a strong, good soldier, looking well, with a healthy appetite and a very good digestion. After his dentures were repaired, his gastric complaints ceased. At this time two Wassermann examinations were made and both were negative. He was then discharged from the Army Hospital. In his letter to Ritter he enclosed a photo taken with his wife and seven children to indicate his condition.

Ritter stated that as early as 1906 he had reported on his experiments on the possible effects of induced hyperemia by the cupping method. At that time he "wanted to establish whether hyperemia is as destructive to tumors or even the origin of growth as it was believed to be." Earlier Bier had tried to influence inoperable tumors with injections of heterogenous blood, a method which he later used locally with successful results. Ritter noted, however, that it was questionable whether the hyperemia alone or whether the heterogenous poison was the cause of the therapeutic success. As early as 1897, Bier tried to induce pure hyperemia locally with congestion of tumors, but with negative results: two cases of sarcoma rapidly spread under this treatment.

In his own cases, Ritter used the suction cup method, "the hyperemic reaction of which there is no doubt." The 10 cases he reported at the time "were all most unfavorable, in the terminal stage (with cachexia, in wretched condition.) In spite of this there was no evidence of increase in size, spreading or proliferation of the tumors. On the contrary, in a series of cases a clear and essential regression of the tumors was observed, the longer and more aggressively he treated the patients." During the course of treatment, portions of the tumors were excised for microscopic

examination. In these cases the originally carcinomatous tissue showed granulation tissue with only a few cancer cells.

Ritter added: "Naturally, I did not succeed in producing great therapeutic successes in these cachectic inoperable cases" (which were the only ones available for such treatment) "so I reported these none-the-less very interesting observations in a very modest form, proving that hyperemia is not harmful. . .but on the contrary, acts very advantageously."

Ritter stressed the importance of the permanent result which was obtained in the above case and observed that today perhaps in a similar case radium would be used. He added: "the fact seems notable to me that with both methods the tumors are slowly destroyed without causing rapid necrosis, softening, sloughing or ulceration. . . . That hyperemia was the cause of healing in such a clear-cut case as ours cannot well be disputed. That it is also an important factor in the regression of malignant tumors, with radium, should be clear to us today, when erythematous inflammatory reactions are so often seen following radiation. (Ritter, 1917; cited by Willy Meyer, 1931)

Ritter had originally reported this case in 1907, in the same journal. In objectively trying to appraise the case he stated that the following objections might be raised:

- a) that the tumor might have regressed spontaneously.
- b) that the incomplete operation, not the hyperemia, was responsible for the recovery.
- c) that it was not a sarcoma. Concerning these objections he stated: "it is well known that a sarcoma disappears by itself, although this is always an unusual rarity, and is disputed by some pathologists. Never, however, has one seen a sarcoma disappear after incomplete operation. On the contrary, this procedure often stimulates the growth of a malignant tumor. As for the last objection, there was no clinical or pathological evidence pointing to a different disease; there was nothing characteristic of tuberculosis or lues. The whole behavior and appearance of the tumor was only that of a sarcoma. The microscopic as well as the surgical findings proved it to be a sarcoma. (Ritter, 1917)

DIAGNOSIS: Four-times recurrent neurogenic sarcoma of the right thigh.

PREVIOUS HISTORY: H.J., male, aged 48. The date of onset was not recorded.

SURGERY: From 1924 to 1929 the patient had four operations for a mass lying beneath the skin of the anteromesial aspect of the thigh. Each time recurrence developed.

CLINICAL COURSE: The patient came to Memorial Hospital on December 3, 1929. Chest films at this time were negative for metastases. No inguinal nodes were palpable, but there was a recurrent mass 3 cm. in diameter lying over the saphenous vein.

INDUCED INFLAMMATION: On March 3, 1930, 3 minims of mustard gas solution were injected intratumorally. One week later, there was an intense skin redness, board-like induration, heat and tenderness extending from the site of injection on all sides for a distance of 20 cm. The reaction was of a very intense nature, precluding the use of more than 3 drops at one time. This gradually subsided, leaving an opening which drained serosanguineous discharge. Portions of the tumor were occasionally extruded through the small slough of skin.

CLINICAL COURSE: By October 13, 1930, eight months after inflammation had been induced, there remained a thin disc-like lesion which the authors believed was "in all probability a completely devitalized tumor, now replaced by fibrous tissue." In reporting on their experiments on animals and patients with this substance the authors suggested that a cure may have been obtained in this case. (Adair and Bagg, 1931)

Willy Meyer (1931) discussed the role of inflammation and artificial hyperemia in the treatment of cancer. He stated that fever is symptomatic of acute inflammation. Bier (1921) has observed: "Inflammation and fever are so closely connected that they have to be called inseparable. Both are reactions of the body to injury involving the destruction of tissue and to irritation from the decomposition products of this destroyed tissue."

According to MacCallum inflammation "consists essentially of the flooding of the injured tissues with an excess. . . of the fluids in the blood." There is, however, and acute inflammation, of which Bier says: "Tissue undergoing chronic a difference in the character of the edema in chronic inflammation acts. . . as a filter and retainer of noxious substances circulating in the blood. Consequently the nature of chronic edema is destructive, while that of acute edema is curative."

Pursuing this observation, Bier since 1900 attempted in many ways and for remedial purposes, to render edema acute. In this connection he speaks of remedial fever and remedial inflammation.

Tuffier (1910) reached the same conclusion when he stated that: "cancer must be killed by drowning." Theilhaber and Edelberg (1913) wrote: "The healing of a carcinoma calls for a more plentiful supply of body fluids to be brought to it."

Willy Meyer agreed with this approach. He noted that the first physician to induce artificial inflammation in cancer patients was Thiersch in 1866, when it occurred to him that saturation of a malignant tumor and the surrounding tissues by fluids could be brought about artificially through inflammation caused by injected chemicals. His first case was a great success. (see above)

At Thiersch's suggestion, Nussbaum of Munich took up the method. Others followed so that in 1867 Volker was able to report on 22 cases.

Volker reasoned that the injected chemical mixture could not be the active destructive agent of the malignant parenchyma, because he found plain water was just as effective. He believed that the injury to the tissue in the sites of injection (the needle path) was responsible for the inflammation to which neoplastic tissue succumbed, and agreed with Nussbaum in demanding complete and uniform saturation of the tumor with edematous exudate as the condition for success in this type of therapy.

Confirmation of the correctness of this theory was furnished years later by Spude who obtained inflammation of the tissue and serous saturation of the tumor by injection of chemically inert material and thus transformed malignant tissue into scar tissue in cases of rodent ulcer of the scalp and face. At first he used injections of aqueous solutions of finely powdered magnetic ore around the tumor, then brought an alternating current magnet into play upon the injected area for 10 minutes at a time, the idea being that the oscillation and heating of the ore particles caused by their repeated magnetization and demagnetization 20 times a second (cycles of alternating current) would be a strong irritant. The result was an enormous inflammation, lasting several hours, with discharge of drops of serous fluid from the tumor. The treatment had to be repeated about 60 times in four months to effect complete regression, and "made great demands upon the patience of both the patient and the doctor." The tissue would become tolerant of the irritation obtainable by this means, and intermissions of one or two weeks' rest had to be made.

Spude, therefore, tried another approach: in a case of carcinoma of the cheek and lip, he curetted the affected areas, then brushed pulverized iron ore on the raw surfaces and pricked the whole area thoroughly with sewing needles. The end-result was the same. (He believed finely crushed quartz sand would do as well.)

Willy Meyer (1924) observed the disappearance of an epithelioma of the nose under the symptoms of artificially induced hyperemia and inflammation produced by means of radium: "The tissue reaction was considerable. For a while the focus on the nose had a rather ugly appearance, discharging sero-pus for several days. Gradually the epithelioma melted away never to return."

Similar results were seen in a number of cases of epithelioma and keratosis of the forehead, cheek, chin, scalp, etc. in middle-aged or older patients: "Under symptoms of local hyperemia, the tumors gradually disappeared with and without slight discharge. Not even the vestige of scar remained. It is interesting, perhaps significant, that a few brief sessions on four to five consecutive days with a comparatively small amount of radium (10 mgm.) brought these results. It seemed to be just

enough to induce a pronounced local inflammatory redness only. This affected the disappearance of the tumors which did not return." (Willy Meyer, 1931)

"Despite the probable inflammation-proof nature of the tumor parenchyma, the tumor as a whole, can become inflamed and therefore, one way of saturating a tumor with exudate, thereby. . . causing regression of the tumor, would seem to be the employment of means of artificial production of an inflammation in the stroma and in the tissue surrounding the tumor." (Willy Meyer, 1931)

Segale's experiments indicated that the local inflammation produced experimentally by breaking a femur in an animal caused an increase in the local temperature of $5\frac{1}{2}^{\circ}\text{F.}$ (3.1°C.) Meyer stated: "The correctness of the conception of inflammation as a local fever would thus seem to have been proved and thus also the association of inflammation with local acidosis."

Meyer then discussed Ritter's use of suction cups, which we have just cited:

"Ritter (1917) produced the complete cure of an extensive sarcoma by artificial hyperemia produced by means of small suction cups. Having tried this method in 10 desolate cases and having, by biopsy, established that under this treatment, carcinomatous parenchyma was replaced with granulation tissue, Ritter had recourse to the method in a robust brick-layer, age 20, who came to his clinic with an extensive tumor of the neck and one of the shoulder. The tumor was soft, almost spongy, blue in color, and had numerous enlarged veins. The laboratory reported: 'no tuberculosis; Wassermann negative. Diagnosis: sarcoma'. An attempt on April 6, 1907, to remove the tumor failed. Beginning on April 12, the tumor was thereupon treated with artificial hyperemia. Small suction cups were applied in daily sittings. Regression of the tumor soon became noticeable. On April 29, it was marked. On May 12, 1907, the patient left the hospital apparently cured. No traces was left of the tumor. Both shoulders looked alike. By accident, the man was met with again on May 6, 1917. In the intervening 10 years he had been active in his trade, was married, had children, and enjoyed good health. 'There can be no doubt,' says Ritter, 'that pure hyperemia was the cause of the cure.'" Willy Meyer quoted Bashford (1912), who for many years was

in charge of the laboratory of the Imperial Cancer Research Fund, as stating:

"Cancer cells must be attacked by changes in their environment and be made liable to extinction through the agencies of these changes." (Willy Meyer, p. 383) He was "the first to suggest the attack upon cancer cells by way of the body fluids in which they live". Operation alone should no longer be considered as constituting in itself a curative sufficiency in cancer. It should always be followed by a general systemic treatment as a prophylactic measure against local recurrence and metastases. In the light of our present knowledge there no longer exists any justification for a procedure consisting in operation only, and then trusting to chance that the patient remain well." (Willy Meyer, 1931)

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Two reports exist of the effects of lightning on cancer patients. The first by Eason (1776) discusses the effects on a tumor of the breast and was cited by Brues (1960) as a noteworthy observation.

The second, Allison (1880) is described as follows:

Previous History: R.S., male adult, the patient was a farm laborer living at Langtoft on the Yorkshire Wolds, and had suffered from cancer of the lower lip and chin for about a year. In 1850 he agreed to an operation by Dr. A. Allison, senior surgeon to the Lloyd Cottage Hospital, Bridlington, England.

Concurrent Shock: Before this operation could take place, Allison stated that the patient "undertook to assist a poor farmer for a day in ploughing his land. During this occupation he was struck down by lightning and carried home in a state of insensibility. Both of his horses were killed, and the wooden beam of the plough was split and reduced to considerable fragments."... He noted that the "electrical fluid seemed to form and pass through two small holes in the head band of his trousers, and to make its exit by corresponding apertures." ... (There was a small burn beneath the belt buckle.) "Soon after this occurrence I visited and found the ploughman in a state of great prostration, and emitting a strong odor of ozone, indicating electrical condensation of the adherent oxygen. As soon as reaction took place, I bled him from the arm, which act constituted the whole of the treatment. What seems to be the most astonishing feature in the case is the healing process which was set up in the lip and chin soon after the accident."

Clinical Course: "The cancer gradually lessened and in a few weeks every trace of the diseased structure disappeared, and for 10 years he enjoyed complete freedom from his former suffering and signs of the disease..."

"After this remarkable exemption from all cancerous development for so long a period, the disease reappeared and after a year of intense suffereng, proved fatal: still leaving the inference unaffected, that the imponderable element (lightning) secured for the patient an extension of life, and ten years' relief from the distressing consequences of carcinoma, which circumstances establish my faith in the

therapeutic power of electricity in scirrhour indurations.

This patient's granddaughter, of Drifffield, developed cancer of the larynx in 1879, or almost 30 years after onset of her grandfather's case. This was removed surgically and then treated persistently with arsenic, with satisfactory results.

In reporting this case, Allison stated that he had done so because he was "not aware that the records of the healing art furnish any case of cancer having yielded to the influence of lightning" and he hoped it would "awaken interest in the curative value of electricity in diseases of a malignant type. Many years ago I heard Dr. Golding Bird express an opinion to the effect that electrical sparks drawn from a cancerous structure until an eruption is produced is the only reliable means of cure he could endorse. In confirmation of the theory of the celebrated electrician, I beg to submit an extraordinary instance of the therapeutic freaks of atmospherical electricity in the cure of cancer." (Allison, 1880)

Allison does not give any details as to the physiological effects or symptoms produced by lightning in his case. However, Le Conte in a long and most interesting paper (1884) describes the immediate and late effects of being struck by lightning in many cases, including men, women, children and animals. He gives a number of references. (All the following cases were knocked unconscious.) In one Negro woman, age 40, no marks of injury were found except a burn under the right axilla about 2.5 cm. or more in diameter. In another Negro woman, age 29, the right side of her body was blistered and marked with discolored streaks extending anteriorly on the lower abdomen toward the pubes. A small streak likewise extended along the internal aspect of the right arm. She complained of gastric and bowel pain for three weeks. Her menses which had been regular prior to the shock became very irregular, and the flow much diminished. In another case, a female, aged 70, who had had menopause 20 previously, there was a violent paroxysm of vomiting following return to consciousness, emesis continued for 10-12 hours. She also complained of pain in the region of the stomach and bowels, for at least two weeks thereafter. Also a troublesome sensation of burning in the palms of the hands and soles of the feet. Within two or three weeks a swelling made its appearance under the right foot, which ultimately resulted in exfoliation of the skin (3-4 cm. in diameter). The shock also relieved her completely of a troublesome stranguary which had harrassed her for four or five years. The most significant effect was that menses began after a lapse of 20 years, and they occurred regularly each month for more than a year (up to the time of his report). "The flow comes on with the usual premonitory symptoms. Her mammae have undergone an obvious preternatural enlargement, apparently originating in a sympathetic irritation emanating from the re-establishment of the reproductive functions." Menses had been regular prior to menopause at the age of 45-50. (Le Conte, 1884)

These observations indicate that lightning may produce profound stimuli including "stress" phenomena and changes in the apparently senile genitalia, as well as the more obvious physiological effects such as burns, gastric disturbances, etc. In the process, the patients' ability to deal effectively with a malignant neoplasm may also be enhanced

or reinforced, thus producing regression as reported by Allison.

Comment: On July 28, 1958, five U. S. Army privates were hospitalized after a bolt of lightning hit their squad tent. Their reaction to this experience may be of interest: one man stated: "It felt as if someone was hitting me on the back with a sledge hammer.... A sensation like somebody choking me." Another stated: "It knocked me about four feet.... There was a burning sensation on my back and shoulders and my left arm got stiff." A third stated that his feet felt as if he was standing on hot coals." Another "felt numb...couldn't stand up." (New York World Telegram & Sun, 7/30/58)

The following three observations deal with the effects of accidental burns or actual cautery on cancer patients.

Case 1: Bilateral ovarian papillomata disseminated extensively over the peritoneum.

Previous History: Miss D., female, age 33. The family history was not recorded. Menses began at 15, a regular cycle, of three or four days' duration, always associated with severe pain. She had always been constipated. Except for painful menses and sick headaches, she had always considered herself well until onset, in March 1886, when she began to feel pain in the right ovarian region on reaching or stepping up. She could not lie on the right side. She experienced fullness after eating a very small quantity. Two years after onset she began to have "irritation of the bladder frequently." This continued and her chronic constipation became very much worse. About September 1888, the abdomen began to enlarge with ascitic fluid. In March 1889, she first consulted a physician who made a diagnosis of "gas and water in the bowels." The treatment was "turpentine, blue pill," etc. In November 1889, Dr. Mary Carleton was consulted and a diagnosis of ovarian tumor was made. The patient was referred to Dr. Frank L. Burt of Boston, Mass. She did not consult him until March 1890.

Heat Therapy: During this intervening four-month period, the patient took about 75 vapor baths. These reduced the ascitic fluid somewhat, and "made her feel better."

Surgery: In March 1890, Burt diagnosed ovarian tumors and advised surgical removal. He operated on April 20, 1890. On opening the peritoneum about two quarts of fluid escaped. On the right side a cyst the size of an infant's head was found, which proved

to be a papilloma with partly fluid contents. A similar growth (about half the size) involved the left ovary. The omentum and bowels "were studded with thousands of papillary masses. The omentum was considerably thickened, and both omentum and bowel presented a very congested and angry appearance." These conditions were considered by the seven physicians present to indicate an absolutely hopeless prognosis. A bilateral oophorectomy was performed in the usual manner. The cavity was thoroughly washed out with boiled water to get rid of as much debris as possible. Numerous small pieces of tumor were washed away. The wound was closed over a very small rubber tube which was left in place 48 hours.

Concurrent Inflammation: The patient received an extensive burn on the right thigh from a hot-water bag following her return from the operating room. This took several weeks to heal and did not present a healthy appearance much of that time. Burt stated: "I cannot but feel that it was beneficial to the patient. I do not, however, under similar circumstances, recommend quite so extensive a counter-irritant if indicated at all."

Clinical Course: The patient made a complete recovery. She gained 20 pounds in weight. At examination a year after operation there was no evidence of recurrence of the tumors or the ascites. She remained in perfect health when Burt reported the case in September 1891, 15 months after operation, and 5½ years after onset. (Burt, 1891)

Case 2: Inoperable carcinoma (cancroid) of the uterus; (no microscopic examination) confirmed by the clinical and macroscopic findings at incomplete operation by Drs. Lomer, Schrader and Niemeyer who stated that its malignancy was undoubted, due to the extensive infiltration into the parametrium.

Previous History: Frau R., female, age 31. Onset, beginning in November 1892 she began to have irregular hemorrhages from the uterus. The whole vagina was filled with soft cancroid carcinoma, which bled easily when touched. The extent and origin of the growth could not be determined. The patient was admitted September 9, 1893, 10 months after onset.

Surgery: Dr. R. Lomer, of Hamburg, Germany, attempted a hysterectomy. The growth

had to be removed by morcellement. It was found that it had infiltrated behind and around the vagina, as well as into the right parametrium. Lomer believed the operation should be terminated, but the hemorrhage was so abundant that he decided to go on. The growth was very soft and friable and repeatedly the retractors were torn out, and on the right side a large opening in the parametrium was made with ragged, crumbling walls. The operation was then completed and the vagina packed with iodoform gauze. The patient left the operating room pulseless and therefore, hot water bottles were placed on her legs.

Post-Operative Inflammation (Severe Burn): From one of these bottles she received (while still anesthetized) a deep third-degree burn almost the size of one's hand. The post-operative course was uneventful, but two weeks later the burned area was covered by a hard dry leathery scab. The patient had not felt any great pain, nor complained, and the nurse had successfully hidden the burn from Lomer's attention during these two weeks. However, she could neither stand nor walk because of this burn. For many weeks Lomer attended the patient at her home, after she was discharged. The burn was dressed with camphor compresses and the limb was elevated.

Clinical Course: On March 13, 1894, she was again seen by Lomer who stated that he was "surprised to see her not only alive but flourishing and to find that the scar was absolutely free from recurrence." She was again examined in September 1899, stating that she had never been in better health and had not needed a doctor since her recovery. She worked hard, delivering bread, arising at 4 A.M. and climbing many stairs; she stood this strenuous life well, and had become fat. Lomer found the vagina smooth and the abdominal region entirely free from recurrence or metastases. The scar of the former burn had shrunk to a diameter of 11 by 6 cm. This patient was in good health and free from recurrence when last examined by Lomer and three of his colleagues in July 1903, over 10½ years after onset. (Lomer, 1903, pp. 344-346.)

In reporting this case Lomer wondered if the burn had had a beneficial effect on the carcinoma, citing the fact that severe burns produce toxins. He asks if such toxins may be antagonistic to cancer. He studied the whole literature on burns, concluding that red blood cells are destroyed by burns and other profound alterations of blood and toxins are produced.

Chrobak (1906) used cautery (actual or fluid, i.e. fuming nitric acid) in treating inoperable cancers of the cervix. He stated that the scab is ^e thrown off in two to three weeks leaving a granulating surface whose healing can be promoted with iodine or silver nitrate. Suspicious points can be treated again. He reported that he had performed 408 such procedures in 10 years to 1900, and that seven patients were living and well three to eleven years after surgery.

In the following case, a severe sunburn appears to have caused temporary regression of a malignant melanoma:

DIAGNOSIS: Malignant melanoma primary in the skin overlying the spinous process of the first thoracic vertebra with a lymph node metastasis in the right posterior cervical triangle, confirmed by microscopic examination following radical neck and axillary dissections at the Mayo Clinic.

PREVIOUS HISTORY: Male, aged 31, civil engineer. The family and early personal history were not recorded. In April 1965 the patient noted that a nevus which had been present since birth had increased in size and had become alarmingly darker in color. He consulted a physician who was also concerned and who took a photograph of the lesion. (Fig. 1)

CONCURRENT SUNBURN: Because of a recent very severe sunburn acquired in Mexico, the patient was advised to return for excision of the nevus after subsidence of the acute inflammatory process (erythematous reaction to the sunburn).

CLINICAL COURSE: At about this time the patient rubbed and scratched the lesion. Because it seemed to disappear, he dismissed all further thought of it until early November 1965 when a mass appeared in the right posterior cervical triangle. This grew rapidly for one month and during the next month it remained relatively stable.

AND INFECTION:

VACCINATION: In early January 1966 the patient was given a small pox vaccination in the right deltoid area. Examination at the Mayo Clinic that month revealed a hard, fixed 2 cm. mass in the right posterior triangle, and a pale slightly atrophied area of skin at the site of the lesion which had disappeared. Careful examination for other sites of primary malignant melanoma, including ophthalmological examination, revealed no other source of a primary lesion. There was an erythematous area over the right deltoid muscle, the site of the recent small pox vaccination, with evidence of slough and secondary infection in this area.

SURGERY: Excisional biopsy of the cervical mass revealed malignant melanoma. Right radical neck and right radical axillary dissections were then performed, with wide excision of the site of the original nevus. Pathological examination revealed only a solitary cervical lymph node involved by the neoplasm. All other nodes, both cervical and axillary, showed non-specific inflammatory changes. The involved cervical lymphnode was almost totally replaced by solid sheets of tumor cells. In

the skin lesion a band of subepidermal fibrosis, with prominent vascular channels and a scattering of chronic inflammatory cells was present in the upper dermis. Numerous pigment filled macrophages were clustered about the area. No definite residual malignant cells were found, although a rare degenerating atypical cell was present in the junctional zone of the epidermis.

PROPHYLACTIC CHEMOTHERAPY: The patient was given sarcolysin as an adjuvant to surgery (50 mg. orally every 12 hours for 36 hours.)

CLINICAL COURSE: Convalescence was uneventful. The patient remained entirely well when the case was reported in 1966. The disease reactivated in June 1966, presenting as a metastatic nodule on the posterior chest wall. Subsequently metastases developed in the left kidney, right shoulder, right arm, right buttock and left chest wall, and there was an enlarged node in the left axilla.

FURTHER SURGERY: On June 27, 1967 one of the last localized lesions in the left chest wall was excised. The left axillary nodes were also removed and showed no evidence of metastasis.

RADIATION: Palliative x-ray therapy was given for relief of pain due to the renal metastasis, without apparent benefit.

CLINICAL COURSE: The disease progressed, causing death on December 24, 1967, 2 3/4 years after onset. (Todd et al., 1966; New York Cancer Research Institute Records)

COMMENT: In this case radical right cervical and axillary lymph node dissections removed the tissues which presumably had received the most obvious immunological stimulus and which might have helped to prevent further activation of the disease. Possibly if only the involved node had been removed, thus preserving the lymphatics which showed non-specific inflammatory changes, the disease might not have reactivated. It is believed that both the sunburn and the vaccination helped to produce the inflammatory changes seen in this patient's lymph nodes.

The following physicians used heat, actual cautery, electrocautery, or "Surgical diathermy" in treating uterine or cervical cancer and cancer of the rectum. This method apparently induced a salutary inflammatory reaction in the tumor bed, and yielded better results than surgery alone.

Diagnosis: Recurrent carcinoma of the uterus.

Previous History: Female adult. The patient had been operated for uterine cancer; local recurrence developed after operation.

Cautery: The recurrence was treated by actual cautery with apparent cure by Ziemssen.

Clinical Course: The patient remained free from further recurrence or metastases until her death from other causes, 17 years after operation; autopsy showed no signs of malignant disease. (Wells, 1909, p. 1735)

Westermarck, of Stockholm, Sweden, devised a method of applying local heat in the treatment of inoperable cancer of the cervix. His apparatus was originated by Berlien, a pupil of Welanders, in 1895. Westermarck modified it somewhat and called it a hydrothermostat. The illustration in his report shows a metal tank in which water was heated and from which it flowed through a rubber tube. The portion of the tubing which was placed in the vagina was wound around in spiral form and then returned to the tank, to be reheated by constant flow. The temperature of the vaginal portion of the tube was 42.5°C. The following was reported in some detail by Westermarck (1898).

Diagnosis: Inoperable extensive, ulcerated cancer of the cervix.

Previous History: Female, aged 50. The patient was married and had a child 13 years previously. She had always been well until onset in May 1897, when menses became irregular, and there developed a copious meat-gravy type of discharge. In August, 1897 severe pains occurred being localized in the region of the left hip. The discharge then became very offensive. The patient was admitted to the Sophiahemmet Hospital in Stockholm on October 24, 1897. In the portio vaginalis an ulcerating carcinomatous growth was found. The left portion had already been entirely destroyed by the growth which extended from the left fornix to the left vault of the vagina and to the left para-

vaginal and parametrial tissue so that the uterus and vagina formed one compact mass with the pelvic bone. The discharge from the ulcerating portion was of an offensive odor. The patient was weak and appeared cachectic.

Cautery: On October 26, 1897 the cancer was energetically curetted and cauterized with thermocautery. The vagina was then packed with "xeroform" gauze which was removed the next day. By October 30, 1897 the ulcerated area was again offensive.

Heat Therapy: About November 1, 1897 Westermarck began heat therapy with his special apparatus described above.

Clinical Course: During the next week the discharge was very copious. Scabs fell off the ulcerated area and the wound granulated beautifully. After a month the patient was discharged, with the ulcerated area completely healed, the pain gone, the general condition improved. However, there remained an infiltration in the parametrium.

Westermarck stated that this was the only case in which his treatment caused complete healing of the ulceration, in the others there was no specific tendency to heal, although there was "nice granulation." He believed the reason why the above case was most successful was because this woman was very cooperative and patient, and tolerated a higher degree of heat than the others. (Westermarck, 1898; cited by Lomer, 1903, p. 332)

In the following case fulguration was used locally and injections of thymus emulsion were given to stimulate systemic resistance.

Diagnosis: Recurrent scirrhus carcinoma of the right breast with no lymph node involvement, confirmed by microscopic examinations after both operations at Mt. Sinai Hospital, New York, by Dr. F.S. Mandlebaum.

Previous History: Mrs. X., female, age 58, the mother of five children, had suffered for years with symptoms pointing to cholelithiasis. Although sharp attacks of colic were not a feature of the case, its chronicity and discomfort caused her son, a physician of unusual scientific ability, to urge operation, as he had a well founded fear of malignant degeneration from gallstone irritation. In April 1904, Dr. Howard Lilienthal performed a cholecystectomy, removing a small gall bladder whose walls tightly hugged a few large calculi, the viscus contained no bile. After convalescence the

patient found herself well and remained so for three years. She then developed a carcinoma of the right breast.

Surgery: Lilienthal performed a radical mastectomy on July 25, 1907. The operation was a very extensive one and healing was slow but complete.

Clinical Course: The patient returned to Lilienthal 18 months later with a nodule the size of a filbert just in front of the anterior axillary line at the level of the seventh or eighth rib. The adherent skin was a little reddened. The indurated mass could be shifted to a limited degree, but was apparently fixed to the underlying structures. A few fine friction rales suggested that the pleura beneath had already been involved.

Further Surgery: With the help of local anesthesia, Lilienthal removed the main portion of the tumor, without invading the ribs or pleura. He felt that radical measures would probably shorten her life.

Fulguration: The wound was not closed, but was allowed to granulate, so that its base might be treated by fulguration. This was done several times by Lustgarten, using a coil spark, the electrode being the graphite point of a lead pencil.

Clinical Course: The wound granulated nicely, but Lilienthal told the patient's son that he "had little confidence in the outlook."

Thymus Gland Therapy: Under the guidance of Dr. G. L. Rohdenburg, the Gwyer method of hypodermic injections of thymus gland emulsions were given.

Clinical Course: The wound healed with a soft cicatrix, the patient remained free from further recurrence or metastases at least seven years, according to Rohdenburg. Lilienthal regarded it as a very unusual case. (Lilienthal, 1913; cited by Rohdenburg, 1918).

Percy (1916) made a thorough study of the use of heat or fever in the treatment of inoperable cancer. He reviewed the literature briefly, citing Byrne (1897), Clowes (1906), Jensen (1910), Lambert (1912), as well as Vidal (1910).

Percy decided to develop "a method of applying heat to the tumor mass to a degree that would permit the greatest concentration on carcinoma cells with a maximum conservation of normal tissue cells." Among the possible agents which could be used were hot air, hot water, electro-coagulation, fulguration and actual cautery. He dismissed the first two, because the penetration of hot air and hot water is so slight (4-5 cm.), He attributed the effects of fulguration to heat alone, and stated that in comparison with the difficulties of applying the foregoing methods, his own method was free from difficulty and its applicability had no limitations when the malignant process is at all accessible. The apparatus was not at all expensive and was easily portable. It consisted of applying heat with an electrocautery accurately controlled by a rheostat, and applied to the affected tissues.

He warned against too high a degree of heat, which produces charring and prevents the permeation of the heat and interferes with subsequent drainage. When drainage is inadequate the patient may suffer toxemia from absorption of large quantities of necrotic tumor cells. Wasserman drew attention to this in the destroyed tumors in mice. He has shown that if the destroyed tumor in these mice is as large or larger than a hazel nut, the animal dies from intoxication from the lytic cancer cells. Percy stated that in two of his cases he had observed intoxication of this character. In both the pelvis was full of secondary carcinoma following pan-hysterectomy. The heat was applied through the vagina and in both instances there was a perfect primary recovery. However, four days later each of these patients showed signs of failure which could not be explained by any local findings.

Percy began using his method in the treatment of cervical or uterine cancer about 1913. During the first three years most of the cases so treated were very advanced but he found that 90% of these patients were rendered operable by the application of heat. He stated:

"The results in this otherwise utterly hopeless type of case are sometimes sur-

prisingly good. This is especially true if there are no secondary degenerative changes in the kidneys, liver and heart....The heat technic is the only method by which a gross mass of cancer can be safely destroyed. The result of this is an immediate physical improvement of the patient. I am convinced that the activity of the metastasis is inhibited, probably because the destruction of the gross mass permits the natural defensive forces of the body to become more active. Another important fact that can be truthfully claimed in favor of the heat treatment is that the local recurrence, should it develop, is much less active, as is shown by a markedly slower growth. In addition to this, the patient loses her pain, and with it the dependence on morphine."

He added that hemorrhages cease and also the stinking discharge, all of which brings with it a hope that life will be prolonged in comfort and it usually is.

"Of the utterly inoperable cases, the kind with 100% mortality, I have six that lived beyond the three-year limit. One of them died at the end of three years, of cancer of the liver, but with a pelvis free from demonstrable cancer. Of the five remaining alive, one was operated on seven years ago, one four years ago, and the remaining three, three years ago. In none of these cases was the abdomen opened, and in all the high degrees of heat were used. In none of these cases was there any subsequent treatment, with the x-ray, serums or toxins."

He noted that recently he had an increasing number of cases recurrent after a Wertheim or pan-hysterectomy, involving the bladder, rectum, pelvic fascia or vagina, and in these no very appreciable benefit was noted.

Of the less advanced group, Percy had 15 cases alive and free from recurrence two or more years after treatment. "These were treated by a low degree of heat, the abdomen was opened, and nothing was removed except the tubes and ovaries.... Since tying both internal iliac and both ovarian arteries I have had no secondary hemorrhage."

He predicted that with the first and second stage of the disease treated by the heat method there would be a 70% five-year survival rate after one application of heat.

He advised a thorough application of a low degree of heat two or three months before doing a Wertheim or pan-hysterectomy. The "operation will not only be made easier from the loosening of the fixed structure by the heat, but it will therefore be made safer;

but more important than all these, if the structures he removes subsequently with the knife are subjected to complete serial section, and examined under the microscope, in many cases no cancer will be found. In other words, he has performed, possibly, a needless operation.

"There are three important causes for the dissemination of cancer....: the knife ..., the curette,..., and...the more or less rough manipulation of the cancer-infected tissues incident to their removal. The knife and curette are a most effective mechanical stimulant and disseminator of cancer infection..., the tumor growth is excited into new virulence in a most remarkable way. To remove a piece of suspected tissue for diagnostic purposes with anything but the hot knife is a most unfortunate breach of good surgical judgment. As to manipulation, a mass of cancer should always be manipulated, if at all, with even more than ordinary gentleness. One of the great advantages of the heat method is that practically no manipulation of the malignant growth is necessary. Wherever the hot knife goes, cancer is destroyed, wherever the cutting edge of a steel knife touches cancer, it is given a new impetus to grow, and many new points of recurrence appear.

Technic: "Open the abdomen. Only by doing this can uterine cancer be safely and most effectively treated by the application of heat.

2. Use a low degree of heat. If a cauterizing temperature is used in the heating iron, a carbon core is formed in the cancer mass. This inhibits the dissemination of heat.

3. Pass the heating head through the utero-cervical junction to the fundus of the uterus. Keep it in one position until the whole mass contiguous to the heating iron is made so hot that it cannot be held longer in the surgeon's hand when encased in a medium-weight rubber glove.

4. Apply the heat until all the structures that were fixed at the beginning of the application are freely movable. To do less that this must of necessity defeat the object of the treatment, i.e., the complete penetration of all the cancer-infected area possible....(Can be done in the majority of cases)."

Percy felt that one may hope for a large number of beneficial results from this method, judging from those already attained (Percy, 1916).

W. J. Mayo (1913, 1915) praised Percy's method and noted that the use of heat is an ancient practice. He added: "It is now 15 years since I abandoned the cutting instrument for the cautery knife in performing vaginal hysterectomy for carcinoma of the cervix. It is worthy of note that while I had few cures during the period in which the knife was used, I noted a considerable percentage of cures after adopting the use of the cautery. The unexcelled results achieved by Byrnes (see below) in the use of galvanocautery in high amputation of the cervix for carcinoma were probably due largely to the elimination of these causes of cancer dissemination.... We should take into strict consideration the possibility of dissemination of carcinomatous material during operative procedures. A specialized technique should be inaugurated in which carcinomatous processes would be treated as though they were the focus of virulent infection... (so as to) avoid grafting and traumatic dissemination of malignant cells during the course of operation and by proper prophylaxis prevent the possibility of grafting following operation. (W. J. Mayo, 1913)

(1914)

Tennant also discussed the use of Percy's method.

Thus it will be seen that several investigators studied the use of heat locally on cancer, especially of the cervix and uterus. Perhaps the interest and enthusiasm for radiation as an adjunct to surgery in such cases, beginning about 1916, may have been the reason why the use of heat was largely forgotten, except for a brief mention in some of the textbooks.

It is hoped that now and in the future gynecologists will be stimulated to try a combination of heat applied locally, in combination with injections of stable, potent, bacterial endotoxins. Such a combined procedure may well be used in all stages of the disease, in the operable cases, before and after surgical removal, to stimulate the body's defense mechanisms and prevent recurrence by destroying any remaining cells, and in the inoperable cases to facilitate later operation, and in terminal cases to make the patient more comfortable and occasionally achieve marked or complete regression.

Percy's conclusions to his first report (1914) are sound. He stated that he had tried to point out the need for widening the field of investigation regarding the vulnerability of the cancer cell. "It will be of particular interest to make further observations as to the relation of the reaction...(produced in the body) following injections of toxins, serums and vaccines in the destruction of carcinoma. If the primary gross mass of cancer can be rendered innocuous by raising the temperature through the medium of the electric heating iron and the remaining...lymphatic involvement be reached by fever produced by toxins, serums or vaccines, as is emphasized by Vidal, then the dream of the ages on the part of the physician, of doing something with cancer, will be on the road to realization."

Byrne (1895) was the first American physician to advocate the use of electro-cautery for excision of the cancerous uterus, noting that by far the most important benefit of this method was the long period of freedom from recurrence. Several of his cases died of other causes after many years of complete freedom from disease. He noted that the condition of four of his patients traced from 4 to 20 years after operation "was so unpromising at the time that no permanent benefit could be reasonably hoped for."

He attributed the results to the effects of heat on the outlying structures. "In no other manner do I think it possible to explain certain phenomena following these operations by galvano-cautery, e.g., (1) the absence of fever and almost all pain, pelvic or peritoneal; (2) the almost universal immunity of the scar tissue after cauterization from secondary attack in the event of recurrence; (3) in the event of recurrence, the long respite obtained from reappearance of the disease in remote parts, even in the most unpromising cases of undoubted circum-uterine infiltration.

"It would appear that utero-vaginal structures which have been severed by galvano-cautery or from which diseased portions have been excised by such means, are left in a state more favorable to a normal, or at least a healthy condition, than where scalpel or scissors have been employed....Gynecologists who fail to take advantage of a method so safe, and yet so promising, assume the grave responsibility of withholding from

the afflicted the most reliable means through which a cure or at least a long respite from suffering and death may be reasonably assured." (Byrne, 1895)

Strauss, et al (1935) reported on their experiences with surgical diathermy of carcinoma of the rectum and colon.

He first used the method about 1913 for the removal of two cancers of the colon and three of the rectum in very old patients. The results were excellent. For years he and his associates used it when operation was impossible because the tumor was fixed, or the patient very old, or when there was some other contra-indication to a radical surgical procedure, such as disease of the heart or lungs. The results were so satisfactory that beginning in 1928 they used the procedure in practically all cases of cancer in the rectum up to the sigmoid colon which could be reached from below by the glass tube method.

"Clinically the results were remarkable. After the first or second application of diathermy the patient gains weight, and the hemoglobin content and the red cell count of the blood are increased to normal levels. Even a patient who has lost a great deal of weight or is cachectic loses all the appearances that are characteristic of a person with advanced carcinoma. The gain in weight shown by our patients has amounted to from 15 to 50 pounds (6.8 to 22.5 Kg.). This increase in weight, red cell count and hemoglobin content is not temporary. We have observed a number of patients for from three to six years, and they have retained their weight, color and healthy appearance..., all the patients received diathermy alone -- no treatment with radium or high voltage roentgen radiation and no liver therapy or other measures to improve the blood picture. Moreover, the improvement cannot be due to colostomy, which was performed on some of the patients, for 22 patients were not subjected to colostomy and they have gained as much weight as those on whom the operation was performed.

"....In many of the cases...the patient was well along in years and had a large mass which was fixed and practically inoperable, and there must have been metastases, at least along the lymph nodes in the pelvis. In spite of this, some of the patients show no sign of metastases, loss of weight or cachexia at the end of six or seven

years, and many at the end of three or four years.

"Kolischer (1936) stated that the electro-coagulation not only produces mechanical destruction of the tumor but causes the throwing off into the circulation of certain substances and antibodies which immunize the patient against further progress of the disease. These substances, in all probability, are similar to the end products of treatment with high voltage roentgen radiation or radium. The reaction may be attributed to an intense stimulation of the reticulo-endothelial system and the consequent local and general phagocytic action of the macrophages.

"...The question is whether surgical diathermy inhibits the further progress of the disease along the lymphatics or in distant organs such as the liver. It is our impression that it does. If it did not, surely some of the patients who were treated for advanced carcinoma three or four years ago would by this time show metastasis in the regional lymph nodes or in the liver. No evidence of such metastases has been observed, however. On the other hand, in two cases in which we explored the abdomen on account of symptoms of disturbances of the bladder, which developed several years after the treatment with surgical diathermy, we removed from the pelvis a few slightly enlarged lymph nodes which contained what appeared to be poorly staining dead carcinoma cells. This indicates at least the possibility that the macrophage and reticulo-endothelial reaction produced by the diathermy may have destroyed the carcinomatous cells in the regional lymph nodes or rendered them inactive.

"In four cases we excised the scar in the rectum resulting from the surgical diathermy by a modified Kraske operation. In one case the excision was made five years after the diathermy treatment; in one three years, and in two, two years....

"The excised scar was examined histologically. In two cases no carcinoma cells could be seen, but in the other two there were definite carcinoma cells. More than two years has elapsed since the excision of the scar in these cases, and there has been no recurrence. The histologic sections appear to consist of degenerated carcinoma cells surrounded by a great deal of connective tissue; according to the pathologist they looked like dead carcinoma cells. This corresponds to the clinical fact that two years after excision of the scar the rectum is perfectly smooth, even in the two cases in which

carcinoma cells were seen in the scar."

Duration and Effects of Surgical Diathermy: Of the 42 patients in their series, 32 had a temperature ranging from 100.6° to 103°F. for several days. The fever usually subsided in eight or nine days. Nineteen had one, eleven had two, seven had three, and five had four diathermy treatments.

End Results: Two of the 11 deaths in the series could be considered as the immediate results of surgical diathermy; two were due to sepsis, as a result of too thorough diathermy, about a year after treatment, and seven were due to other causes, coronary or cerebral hemorrhage, embolism, or pneumonia. (Three patients had undergone an operation for cancer such as removal of the sigmoid or transverse colon, and in three patients the carcinoma of the rectum was probably metastatic.)

The other 31 patients were in excellent condition, one after seven years, two after six years, nine after four years, and twelve after three years or less. They gained weight and did not look like patients with cancer. Twenty-two of them had full use of the rectum (they did not have colostomies).

The authors noted that they had collected reports of 25 similar cases treated successfully by other surgeons in the previous two years.

They then described their technique..., noting that they had been able to coagulate tumors as high as four to six inches above the anus.

Early in the work they coagulated too deeply and too thoroughly. They then found it best to coagulate superficially and then wait two or three weeks to see how much has been destroyed, and then give a second, third or fourth application if necessary, at intervals determined by rectal examination. In this way much less stricture or scar formation resulted -- in a number of cases there was none.

In five cases there were severe hemorrhages requiring packing (none of them fatal), which usually occurred from 8 to 12 days after treatment, during the period of sloughing. In two cases it was so severe that transfusion was required. In one case a rectal abscess developed.

Conclusions:"We lay great stress on the fact that in 22 cases excellent results were obtained without colostomy, the patient having full use of the rectum.

We are great believers in the radical and segmental removal of the entire ascending, transverse or descending colon for carcinoma, especially when the continuity of the bowel can be re-established and the patient can defecate normally. It is, however, quite another matter to remove the lower part of the sigmoid colon and the rectum and leave the patient with a permanent colostomy opening. While it may be gratifying to the surgeon to demonstrate a series of such cases many years afterward, we do not believe that many of the patients are happy.... How much better it will be if by surgical diathermy the rectum can be preserved with its full physiologic function and the patient can live as long as the one who has a permanent colostomy....

"We are particularly interested in the method since it is the first one in which local destruction of, or local application to, a carcinomatous growth has produced, clinically at least, a permanent effect.... This reaction is probably being brought about by an intense stimulation of the reticulo-endothelial system. What the substances are that are liberated into the systemic circulation or into the body by the destruction of the carcinoma by diathermy is an interesting subject for further research."

Strauss and his associates have continued to use this method and reported in 1956 that in the preceding 40 years they had treated about 250 rectal cases this way with excellent long term results. (Strauss, et al, 1935; cited by Lehmann, 1955) In 1969 Strauss reviewed his experiences with this method over a 50 year period in a monograph

Another physician who reported on the beneficial effects of electrocoagulation combined with injections of macrophages, was Kolischer (1936), who recognized the need for a constitutional treatment of cancer. He believed that surgery and radiation will in time be only adjuvants to cancer therapy. He stated that "For centuries all attempts at curing cancer were based on the principle of destruction without paying any attention to constitutional factors. As all attempts at discovering one single cause of cancer resulted in failure, it became more and more evident that the production of cancer is based on a multiplicity of factors, some essential and some of a

contributory character. . . .We are compelled to acknowledge a general and a local predisposition toward the development of cancer. Millions of people are exposed to the same noxae and yet a minority only of individuals produce cancers. . . .Predisposition is a constitutional proposition. Therefore, a great many biologists and pathologists lean toward the theory that cancer, even in its initial stages, presumes a constitutional derangement which under certain provocative influences leads to its local manifestation - the cancerous tumor. . . ."

Kolischer noted that in certain instances a combination of radiation and electrocoagulation showed a pronounced improvement in results over radiation alone. Extensive inoperable tumors were successfully coagulated while at the same time primary mortality and surgical shock were materially reduced. Encouraged by the results obtained by electrocoagulation of cancers of the portio, cervix, rectum and bladder, some surgeons extended the field to cancers in organs of the thoracic and abdominal cavities. This was accomplished either by the esophagoscope or by opening the abdominal cavity and anchoring the tumor to the edge of the incision and then proceeding with the electrocoagulation. In the majority of cases clinical cures were obtained even in tumors which were absolutely inoperable by ordinary surgical procedures.

It was first observed, in electrosurgery applied to vesical cancers, that in some instances incomplete destruction of the tumors by electrocoagulation furnished complete and permanent cure. Similar observations were made in cancers of the tongue, cervix and rectum.

Kolischer then discussed the reasons for such results: "To the biologists it has been known for a good many years that there exists in the human and animal body a well-defined system of specially endowed cells (the reticulo-endothelial system) in which reside practically all the defensive forces of the body, and that these cells play a predominant role in combating cancer. The active elements of this system, the macrophages, are of migratory character and may be attracted to any part of the body in which an increase of metabolism occurs. Clinical and experimental research has shown that to the area around the zone of electrocoagulation there occurs an abundant

immigration of these macrophages. The activity of these cells explains the successful results following incomplete destruction of neoplasms by electrocoagulation."

Kolischer cited the studies of Cramer and Crabtree on the therapeutic action of radium on spontaneous mammary mouse carcinoma. They found that in radiosensitive tumors the reaction begins with the invasion of stroma by macrophages. In radioresistant tumors radium does not produce this migration.

These observations indicate that radiosensitivity is not an inherent quality of the cancer cell, but depends on the surrounding stroma which in turn is influenced by the action of the macrophages.

It is also known that in a number of individuals there prevails a functional and productive deficiency of the reticulo-endothelial system. Kolischer believed therefore that the next logical step was to attempt to assemble macrophages outside the body and place them in a vehicle so they could be injected as an emulsion around the tumor.

Horn, under the direction of Saphir, succeeded in developing such a method in the Research Laboratory of the Michael Reese Hospital, Chicago, Illinois. Macrophages were segregated from the spleens of animals with a Rosenow tissue press and were suspended in a Tyrode solution in which they remained alive from six to eight hours. Experiments on tumor-bearing rats were so encouraging that the method was tried on human patients. Such injections led in numerous instances to complete disappearance of the tumors. In other cases inoperable neoplasms became so reduced in size and so movable that they could easily be enucleated. That invasion by macrophages following their injection around tumors led to the inactivation of remaining cancer cells, was proven by the histologic examination of specimens removed four years, two years and one year after injection. In the center of the specimen cancer nests were found surrounded by numerous macrophages, but no invasion of the surrounding tissue by cancer cells was observed. In ulcerated cancers the combination of electrocoagulation with cell injections accelerated the throwing off of the scab and healing.

In conclusion he stated: "In the future will come biologic treatments that will

lead up to the ideal goal: cures without mutilation, and a guarantee against local recurrence or remote metastases." (Kolischer, 1936; cited by Stern, 1941)

Crile (1961-1963) studied the effects of heat as an adjunct to the treatment of cancer, both experimentally and on a small group of patients. In three patients with intracutaneous metastases from breast carcinoma, striking regression followed heat, ranging from 30 minutes at 48°C. to 24 hours at 42°C. Irrigation of a colon cancer with water at 50°C. for 20 minutes combined with radiation, resulted in temporary regression. Similarly, a rectal cancer treated before surgery showed a striking regression after heating (50°C. for 15 minutes). He concluded that some cancers are more susceptible to heat than the surrounding normal tissues, and that further uses of heat should be explored. (Crile, 1961)

He also reported the case of an infant in whom multiple subcutaneous metastases of a neuroblastoma disappeared completely following immersion first of the back, and several days later of the abdomen in a water bath at 45°C. for one-two hours. Regression did not take place in the unheated areas. Biopsy specimens taken three weeks after the heat treatments showed no viable tumor. On the basis of these observations, Crile concluded that the use of heat as an adjunct to the treatment of cancers should be further explored. (Crile, 1963)

It appears that the inflammatory reaction that follows prolonged exposure of certain cancers to temperatures between 42° and 50°C. selectively destroys the tumors without damage to normal tissues. This reaction is potentiated by injections of serotonin into the tumors immediately before they are heated. Since the tumors are transplantable, if transferred to another animal immediately after they are heated, it seems that it is the inflammatory reaction that follows heating rather than the heat itself that selectively destroys the tumor. Sublethal exposure of tumors to heat also greatly potentiates the tissue-destroying effects of radiation.

If the chemistry of the inflammatory reaction were better understood we might be able to use the compounds liberated by heated tissues as adjuvants to the treatment of certain cancers. (Crile, 1962)

In this connection it is of interest to note that the Japanese, who daily take very hot baths submerged to the chin (113°-128°F.) have a very much lower incidence of cancer of the skin, breast and testis - areas in which the heat of these baths could stimulate an inflammatory reaction as well as leukocytosis and thus destroy precancerous areas or incipient cancers before they became clinically apparent. (Bazett, 1924; Burton, 1891; Hill, 1907)

The following six histories are cases of concurrent hemorrhagic pleurisy or ascites:

CASE 1:

DIAGNOSIS: Inoperable atrophic scirrhus cancer of the breast with generalized carcinomatosis, ascites, etc.

PREVIOUS HISTORY: E.L., female, aged 22. Careful examination revealed no evidence of syphilis in the family or previous personal history. Onset, in May 1882, the patient first noticed that her left breast had become painful at the compression of her corset. At this time she found a small tumor the size of a little nut beneath the skin which moved under the fingers. The tumor increased rapidly in size and the overlying skin became adherent. Lancinating pains (not acute) began to be felt in all the breast but they did not radiate widely. About 10 months after onset the tumor was the size of a large egg, and began to ulcerate and discharge a sero-purulent fluid. The patient became very much weakened. The tumor then diminished in volume, the ulceration healed and finally the growth was much reduced in size. Two months later, a year after onset, the right breast became involved and the same symptoms supervened. At this point the patient became markedly cachectic. She took almost no nourishment, had no place to sleep, was exposed to cold, and had developed a persistent cough. She was admitted to the Hotel Dieu Hospital in Paris so weak she could hardly walk, extremely emaciated, with a markedly straw-colored complexion and a dry cough which was very fatiguing. She also had severe abdominal pains. In brief, she seemed to be in a state close to death with advanced cachexia. Physical examination revealed that the tumor of the left breast was the size of an egg, but was flattened, hard as wood and attached to the thoracic wall. Palpation revealed that all the tissues were adherent to each other. There was no longer any mobility between the breast and the overlying tissues or between the breast and the thoracic wall. The overlying skin was greyish, faded and wrinkled, the

classic "orange skin" appearance. From the body of the tumor there were irregular infiltrations along the periphery which invaded the surrounding structures deeply and also involved the skin. There was no ulceration. Over the right breast the overlying skin was adherent but the breast itself was not as hard as the other one. In the left supraclavicular triangle and in both axillae there were painless enlarged lymph nodes the size of small nuts, which moved easily on palpation. There was no pain in the arm but quite considerable edema of the entire upper arm. The hepatic region was sensitive to pressure, and palpation revealed definite nodules deeply situated in this region. The liver was enlarged. In the thickness of the abdominal wall there were six or eight hard flattened nodules the size of peas, giving the sensation of discs fixed in the tissues. In the posterior thoracic wall in the region of the nape of the neck there were similar small metastatic nodules, the overlying skin being normal.

PLEURAL EFFUSION: At this time, November 3, 1883, it was noted that there existed a slight effusion in the peritoneal cavity and a slight pleural effusion, believed to be about 1 to 1½ litres. Vulpian examined the patient and did not hesitate to say that the prognosis was extremely grave, in fact he believed the end to be imminent. Nevertheless, he prescribed tonics: Todd's potion (Tincture of canella, brandy, sirup and water), extract of quinine, sirup of iodide of iron and arsenate of soda. Two days later the patient began to take a little nourishment. There was still some insomnia but the abdominal pains and the cough were less severe. The improvement continued and by November 12, 1883 the patient had a better appetite. On November 20, 1883, she was able to get up for the first time. On December 1, 1883, it was noted that the tumor of the left breast had begun to decrease in size, also the axillary nodes. There was no longer any edema of the arm or of the ankles, nor any appreciable ascites. On December 20, 1883, the patient was discharged having completely regained her appetite and strength. On her return in January 1884, it was noted that her general condition had continued to improve, and that she had never been

better. The tumor of the left breast no longer was protuberant, the nipple completely retracted; the remains of the growth consisted of a flattened disc about 2 cm. thick, of the consistency of wood. The metastases in the abdominal region and dorsal region had completely disappeared, as well as those in the axillae. At the base of the right lung there persisted a marked dullness, the vocal vibrations being absent. The voice was a little resonant. The patient was finally discharged on February 25, 1884, having entirely regained her former good health. This was almost two years after onset.

In reporting this case in 1885 Vulpian stated that there could be no doubt as to the diagnosis; that in spite of the fact that the disease had become generalized, there was almost complete spontaneous regression. He added: "It must be remembered that there was also a pleural effusion. . .diagnosed as a cancerous effusion, a hemorrhagic pleurisy as it almost always is in these cases." (Vulpian, 1885)

CASE 2: Inoperable recurrent ulcerated carcinoma of the breast ("cancer en cuirasse").

PREVIOUS HISTORY: Female, age not given. The patient had twice been operated for recurrent cancer of the breast in 1895 and 1897; the final recurrence involved the chest wall and axilla with extensive ulceration. There was enormous edema of the arm, and the patient was cachectic.

CONCURRENT INFLAMMATION: In 1899 she developed hemorrhagic pleurisy (2 litres). No details are recorded.

MEDICATION: Beginning in August 1899 subcutaneous injections of sodium cacodylate were given in doses progressively increased to 0.75. Thereafter this dose was maintained and given every 15-20 days for 7 months. The ulcerated area healed, the metastatic nodes regressed, the patient gained weight and strength, and at her own request she was discharged.

CLINICAL COURSE: She remained thus in September 1901, six years after the first operation, according to Tuffier (1910, pp. 19-20), who reported the case. Tuffier was the first to deliberately induce fever as a therapeutic measure in a cancer patient, according to Willy Meyer (1931, p. 343).

In the following case ascites occurred rather than pleurisy:

CASE 3: Recurrent carcinoma of the breast (multiple) with extensive metastases in the liver: "the clinical history and the morphology of the tumor were typical of a rapidly growing malignant cancer". The recurrent growths were also examined histologically.

PREVIOUS HISTORY: Female, aged 37. The family and previous personal history are not recorded.

SURGERY: In spite of the fact that a radical operation for carcinoma of the breast was performed, multiple recurrences soon followed and were removed. Others soon appeared in the neck and breast, but on account of local complications and the patient's debilitated condition, were not removed. Later large metastatic tumors appeared in the liver which nearly filled the abdominal cavity.

CHYLIFORM ASCITES: This was followed by excessive chyliform ascites. The prognosis was "unqualifiedly bad and death seemed imminent." However, instead of death ensuing, the patient's condition improved. The tumors in the neck and breast gradually dwindled and disappeared. The abdominal tumors grew smaller and became imperceptible and the liver became smoother and smaller. "At length, about four years after the first operation, the liver is approximately normal in size and position. With the exception of the scars, and decreasing emaciation, and extreme chyliform ascites requiring frequent tapping, there is no indications of the original disorder." (Hodenpyl, 1910)

This case impressed Hodenpyl with the possibility that the ascitic fluid might be tried experimentally. Accordingly, it was withdrawn and injected into tumor-bearing mice. These injections were made near the tumors, into the tumors and into the body at large, resulting in necrosis of the growths, a noteworthy diminution in size or complete disappearance. Having proved the harmlessness of these injections, Hodenpyl tried the procedure on patients. "The general effect

was nearly uniform, in producing a temporary local redness, tenderness and swelling about the tumors, then softening and necrosis of the tumor tissue which was then absorbed or discharged by sloughing, with the subsequent formation of scar tissue. In all the cases the tumors grew smaller, in some they disappeared altogether. In no case did any tissue other than the tumor show the least reaction after these injections, nor were there any systemic effects evident after even large intravenous infusions. The results in the majority of the 47 cases treated were distinctly favorable, many of them being hopeless and inoperable when treatment was begun." (Hodenpyl, 1910, pp. 105-106).

In discussing this case and that of MacKay (see below, case 4), McConnell stated: "In both Dr. MacKay and Dr. Hodenpyl's cases the regression took place after the formation of large collections of fluids within the serous cavities. The tumor masses then begin to degenerate, become necrotic and are cast off or absorbed as the exudate is taken up into the general system. It would seem that after a certain point has been reached there are formed in the patient substances that exert a distinctly lytic effect upon the tumor cells. Dr. Hodenpyl's experiments in using the ascitic fluid as a therapeutic measure indicate that there is some substance present in the proteid exudate that exerts an active influence upon the growth. . .; the curative action of the serum. . .is apparently not of an antitoxic agent as much as it is a lysis of specific cells." (Connell, 1910)

Hodenpyl died in 1910 and we have not found reports of other investigators using this method since then.

CASE 4: Recurrent inoperable scirrhus carcinoma of the breast with metastases in the sternum, the supraclavicular region and the lungs, confirmed by clinical and microscopic examinations of the primary growth and of some of the ^{nodes} lymph_a at the Deaconess Hospital, Edinburgh.

PREVIOUS HISTORY: Female, aged 39. The family and early personal history were not recorded. Onset, April 1903 she first noticed a lump in her breast. At this

time she was in very good health. The patient was first seen by Dr. Charles Gordon MacKay, of Lochcarron, Scotland, in October 1904, at which time she had a typical mammary scirrhus. The diagnosis was confirmed by Dr. Bruce of Dingwall, and the patient was admitted to the Deaconess Hospital in Edinburgh. Examination on admission showed a circumscribed carcinoma in the outer quadrant of the right breast, adherent to the skin, but no lymph nodes were palpable in the axilla.

SURGERY: A radical mastectomy was performed on November 4, 1904. The axillary nodes were involved, but the prognosis did not seem particularly unfavorable. The patient made a good recovery and went home.

CLINICAL COURSE: On January 9, 1906, 14 months later, she returned with small fixed recurrent nodules in the scar, a larger one below the clavicle, and a bulging of the sternum.

RADIATION: As the condition was completely inoperable, the patient was given x-ray therapy to the point of producing reddening and scaling of the skin. The progress of the disease appeared to be arrested. In August 1906 she returned for another course of x-ray therapy. In the interim the disease had progressed and there was an irritating cough, apparently due to the pressure of the metastases on the laryngeal nerve.

CONCURRENT HEMORRHAGIC PLEURISY: There was marked dyspnea and dullness over the pleural cavity on both sides. Thoracentesis yielded 40 oz. of blood-stained fluid from the left pleural cavity and 10 oz. from the right. After this procedure there was dullness up to the lower angle of the scapula on both sides, and there was also dullness of the right apex. A fortnight later, 28 oz. of blood-stained fluid were withdrawn from the left pleura. The breathlessness returned. An attempt was made to tap the left pleural cavity but only a few oz. of blood-stained fluid were drawn off. It was inferred that the dullness was mostly due to the thickening of the pleura and consolidation of the lung as a result of metastases. The patient gradually failed, and made up her mind to go home. She was discharged on November 8, 1906 in a hopeless condition. For several weeks in December she was

in a state of semi-collapse. At this time there was a deep blue discoloration over the whole front of the chest from the clavicles to a line a little above the upper margin of the liver. The left breast was of great size and hard. The left axilla was obliterated, filled with malignant growth, and the right axilla was almost filled. Both sides of the chest contained fluid almost to the clavicles, respiration being 44. Swallowing anything, even a teaspoon of water, was difficult, and at times impossible. This state continued up to and including December 28, 1906. The next morning the condition had entirely altered. The patient was much better and felt comparatively comfortable. She could swallow easily. The respiration had fallen from 44 to 24. The fluid in the chest had practically gone. She gradually took food in greater quantity and improved in every way. Still more remarkable was the fact that the seat of the local disease (the pectoral region) gradually underwent a change for the better quite as great as the general condition. In its whole extent the deep purple discoloration gradually became markedly lighter. In some places the skin regained its normal whiteness, and where it had been tense and shining, it became at first wrinkled, then flaccid.

It was noted that the diseased parts which had not received x-ray therapy had undergone an extraordinary change: the left breast which had grown to a large size and felt hard had absolutely disappeared with the exception of a brownish-yellow circular flat disk the size of a sixpence, of horny consistency and appearance, which occupied the place where the nipple had been. There was absolutely no trace of the mammary gland and where it had been the skin was flat and close to the ribs. The left axilla which had been full of metastases was now a cavity into which Mackay could place his closed hand. The right axilla was the same. The space where the right breast had been and the parts adjacent had all been subjected repeatedly to x-ray therapy, and here the improvement, though quite as great, had gone on at a slower pace. Mackay stated: "Though there is healthy action, the tissues seem to be in a semi-paralyzed state. The x-ray had not been elective in action. It had affected the diseased and healthy tissues in equal

degree."

CLINICAL COURSE: The cough, which had never been absent for 10 months, ceased completely on January 6, 1907, and had not recurred when the case was reported in July 1907. The steady improvement continued in every way. Morphine, which had been administered steadily for some time in 1 - 1½ grain doses, was stopped altogether by February 1907.

In reporting this case, Mackay stated that the patient had been in a half-starving, dehydrated condition, a state most favorable to the absorption of the thoracic exudate. "When the absorption took place, the pressure on the esophagus was relieved, so that swallowing became possible, as well as relieving the lungs, so that respiration fell to 24. However, the improvement, not only general but also local, coincided exactly in point of time with the disappearance of fluid from the chest... .The fluid (serum) had been suddenly, rapidly, and in considerable quantity, taken into the system. It thus came into contact with a malignant growth which at that moment was overwhelmingly master of the situation... .The growth then not only ceased to advance, but actually withered." Mackay believed that a powerful agent in the serum had produced this result. He suggested that patients might be artificially "inoculated" with such a serum. In conclusion he stated that he felt that the victory over cancer will ultimately be through a serum.

In a personal letter to H. Gideon Wells, M.D., of Chicago, Mackay stated: "I described the changes as if the tumors had withered. A closer description would be that it looked as if the tumors had dissolved, and so dissolved, as to become absorbed, leaving nothing but the covering of skin." Wells was much impressed with this case and stated: "Apparently the serum from the cancerous pleura on being absorbed, either itself or else, which is to me more probable, it stimulated the resisting powers of the organism and led to the development of cytolytins for the cancer cells, which caused the rapid retrogression of the cancer tissue." (Wells, 1915, p. 1738)

Mackay informed Wells that this patient died some five weeks after he had read

his paper, or about 14 weeks after the disease had regressed. Mackay added: "She had gone through a very great amount of suffering under circumstances of excessive mental strain, and she died of exhaustion. So far as we could make out clinically the disease had absolutely left her. Whether, if she had lived it would have recurred, is another matter." (Wells, 1915, p. 1738)

In reporting this case Mackay further stated: "There can be little doubt that occasionally a true cancerous tumor comes to a pause in its growth, when it seems in fact to have lost its power of further attack on healthy tissue, and then a cure, more or less complete, is said to have taken place. When this has happened, it is reasonable to suppose that some agent must have been at work either as aiding the body tissues in their resistance to attack, or acting in antagonism to the cancer cell, and so diminishing its invasive vigour. If there be any such active agent, what is it? Is there possibly elaborated in the body of the patient a something which can act in this way and so effect a spontaneous cure?" He believed the above case "seemed to suggest an answer to this question. (Mackay, 1907)

COMMENT: The toxic effects of absorption of such large quantities of necrotic tumor tissue appear to have caused this patient's death. It is of interest to note that the irradiated tissues responded more slowly.

MacCulloch (1908) discussed Mackay's case as follows: "In this, as well as in several cases recorded in England, in Europe, and in America, of spontaneous recoveries from cancer in man, one conspicuous feature that seems not to have been sufficiently appreciated has been the invariable extensive lymphatic glandular involvement - a fact, indeed, which has led to the decision that the cases were inoperable. Such was the condition of the case I have just referred to. . .

"Hitherto, lymphatic glandular involvement in the infectious processes in the animal body has been looked upon most unfavorably both by the physician and the surgeon, as a 'spreading of the disease in to the most vulnerable parts of the system', and not as an extended response of the body in the mechanism of bodily defense.

"These glands which are usually conspicuous in the neck and axillae are therefore cut out as completely as possible, it is said 'to prevent further spread' or 'recurrence' of the malady. It should, however, be noted that there is this serious inconsistency in what has been called the 'radical operation' in cancer, that these glands are usually left undisturbed, when they are not easily accessible to the fingers, as in operations for cancer in the abdominal organs. The fact that these glands have been estimated to number from 800 to 900 in the human subject, and that they exist for the purposes of a most important function, seems to have been entirely overlooked.

"Professor Goldman, in a paper read before the Royal Society of Medicine in November last, stated that the results obtained by the German surgeons who now operate in cancer without extirpating the involved lymphatic glands were no worse than those obtained by other German surgeons who insisted on their complete removal." (MacCullough, 1910; cited by Venus, 1910) Only in recent years have a few surgeons ^{again} begun to express this concern. (Crile, 1965-67; Fowler, 1969; A. Strauss, 1961)

Mackay's case also impressed Wells (1909) who mentioned it in his paper on the resistance of the human body to cancer. Wells admitted even after years of careful, painstaking work, during which radical operative methods have been developed to a high degree of perfection, one is forced to admit that as yet the results from such surgery are anything but satisfactory. The most skillful operators claim at best about 40 percent recoveries in cancer of the female breast, while in cancer of the cervix recovery is exceptional (10 to 20 percent five-year survivals).

He suggested the need of studying the manner in which the body defends itself against the disease, so that we may endeavor to heighten, supplement, substitute or initiate this natural method. He noted that the development of concurrent infections notoriously impedes the progress of neoplasms; also, severe hemorrhages in advanced cancers are frequently followed by improvement.

He mentioned the medieval practices of phlebotomy and the production of chronic

ulcerations on the extremities of cancer patients "to let the cancer humors escape."

He then studied the reports of cases in which malignant tumors had shown healing changes independent of any apparent infection, hemorrhage, change in diet, local nutrition or blood supply.

He cited Mohr (1903), Senger (1903), Crosbie (1899), Rotter (1899), Von Hanse-mann (1902), Martin (1908), as regards carcinoma, and Randolph (1905) as regards sarcoma or endothelioma; Frank Hall (1908) as regards hypernephroma; and Gaylord and Clowes (1906) for chorioepithelioma.

Wells stated: "The evidence concerning the healing of portions of carcinoma left after operation is far better than that offered as proof of spontaneous healing of growths in which no operation has been done." He cites a male who was operated for supposed recurrent appendicitis with abscess formation. A colloid cancer in the region of the appendix was found (but not touched), which regressed entirely following exploratory laparotomy, leaving a fecal fistula. A year later this was closed and examination at this operation revealed no trace of the former growth, but merely a calcified mass from an old appendiceal abscess. This was removed. The patient recovered and remained well and active for 12 years when he developed obstruction and died following anastomosis of the ileum to the colon. A large colloid carcinomatous mass in the cecum caused the obstruction.

Wells cited the experience of Czerny and Pearce Gould's famous case.

As to the value of cauterization, he cited Lomer and stated: "There seems to be a remarkable proportion of success among the cases (of uterine cancer) persistently treated for each recurrence with the actual cautery, a point on which Czerny seems to agree." (He cited Ziemssen's case of recurrent uterine cancer cured after cauterization and traced 17 years.)

"A possible explanation of the retrogression of metastases after operation which I would suggest is autoimmunization. During operative manipulation a considerable amount of cancer juice and cancer tissue is forced into the circulation. Ordinarily, as we too frequently observe, this results in a rapid and widespread

recurrence, but it may happen under certain circumstances that these cancer products stimulate the reactive forces of the organism and lead to an active immunization." He cited Mackay's very important case in support of this. (See above for his comments).

Ribbert had reached a similar conclusion from his studies. He believed that in the case of tumors developing spontaneously, the tissues become habituated to the tumor, and the only prospect of immunization is the sudden overwhelming of the organism with cancer substance which would stimulate the production of antibodies, just as appears to have occurred in Mackay's case. Ribbert suggests injecting cancer extracts immediately after surgical removal in order to induce active immunity and to destroy hidden metastases. (This was similar to Rubens Duval's work discussed earlier).

Wells concluded that the data he had collected indicate that there exists in man natural forces which tend to cause healing of malignant tumors, and the possibility of augmenting these forces is before us, and should encourage us to constant effort toward this end. (Wells, 1909)

DeCourcy (1933) discussed both the Mackay and Hodenpyl cases abstracted above. He stated: "In view of the general conviction in the past that cancer is an incurable disease there has naturally been an inclination in cases (of spontaneous regression). . .to assume that the diagnosis was erroneous - a disconcerting reflection that has led the physician observing the case to keep silent about it, or to place a question mark against his report. There was a tendency to believe that if it could be cured, it was not cancer. . .

"Reports of such cases have become too frequent to be ignored, and they come from too many authorities to require to be called by name.

"There are no accidents in Nature. . . I believe it is of the very first importance to give close study to cases of this kind with a view to gaining an insight, if possible, into Nature's methods of healing and to discover what can be done to make her work easier."

Rohdenburg (1918) published a synopsis of 302 cases selected from the literature, in which the phenomenon of spontaneous regression had been observed. In roughly one-third of these there was microscopic confirmation of the diagnosis and the subsequent history was carefully controlled. In a second group a bare possibility of diagnostic error might be conceded, and in a final group a somewhat greater possibility. In every case the condition was inoperable and hopeless, no radiation had been given, and where operation had earlier been attempted, it was recorded as palliative or incomplete. Yet tumors or metastases unaccountably disappeared and the patients became clinically well... A process that had been considered irreversible was reversed."

Irrespective of whether the cure was permanent or not, the fact of regression for a longer or a shorter period is established.

DeCourcy stated: "I cannot sufficiently emphasize the significance of this fact. It demonstrates. . . that cancer is not necessarily incurable; that the human body is capable of waging a winning fight against malignancy under apparently the most hopeless conditions. It proves the existence of immune forces capable of terminating the disease.

He cited the work of Gaylord and Clowes (1906) with experimental cancer in animals; 23% spontaneously regressed, 95% of these being in tumors less than 1 cm. in diameter.

The frequency of regressions and its distribution in animals led these workers to believe that it might be more common in human beings than is generally supposed. Since cancer as a rule is already old when diagnosed in patients, there is no way of knowing how many cure themselves in their early stages.

He discussed the various defense reactions of the body: sclerotic, lymphoid and inflammatory. The sclerotic reaction introduces a process of fibrosis, with formation of dense cords of stroma rich in fibroblasts and collagen that prevent deep infiltration - a sclerotic barrier is thus erected which tends not only to arrest the onward march of the epitheliomatous masses, but also to circumscribe

the nucleus of the neoplasm. Such a barrier is usually only temporary, being as a rule rapidly overcome by the cancer. But occasionally it insinuates its way between the neoplastic masses, segmenting them off into small groups which then become imprisoned, undergo atrophy and finally disappear. The blood vessels are obliterated in the general sclerosis, with the two-fold result that their invasion by the proliferating cells is impossible, and that a state of anemia is produced in the cancer.

The lymphoid reaction causes a layer of lymphoid tissue of varying thicknesses to appear around the cancer, due to accumulation of mononuclears and to the changing of the connective tissue into a reticulated tissue. It opposes not so much the proliferation of epithelial cells as the diffusion of toxic cancerous substances, and thus stands ready to assist any form of therapy, such as radium, for the success of which the prospect is good.

The inflammatory reaction may represent a counter-offensive of the organism. The polynuclears cause degeneration of the epithelial cells that are still living, and may under some circumstances lead to extensive necrosis, reaching even to the periphery. The carcinomatous island is destroyed, and at that point where this happens spontaneous cure must be regarded as a fact.

He then described Mackay's case as one of the most instructive instances of spontaneous regression of a malignant tumor (see above for full abstract of case), and added: "How are we to explain such a case? The half-starved condition of the patient was evidently a state exceptionally favorable for the absorption of the exudate which was suddenly taken into the system in great quantity. It thus came into contact with the cancer, which thereupon underwent a shrivelling process that ended in its extinction. The connection between the absorption of exudate and the disappearance of the growth was indisputable.

"The relation that may exist between the absorption of an exudate and the recession of a neoplasm is further illustrated by Hodenpyl's remarkable case. Here there was multiple recurrence of mammary cancer, with metastases to the liver,

followed by excessive chyliform ascites. The case was inoperable, but instead of dying the patient improved from her desperate condition, and four years later had no indication of her former disorder except her scars and continued ascites, which required frequent aspiration. Hodenpyl injected the ascitic fluid into cancerous mice, with the result that the tumors decreased or disappeared. Encouraged by this phenomenon he ventured to inject the fluid into no less than 47 human cancer subjects, using large quantities. The general effect was nearly always to induce temporary local redness, tenderness and swelling around the tumors, then softening and necrosis of the tissue, which was absorbed or discharged externally, with subsequent formation of connective tissue. In all, the tumors became smaller; in some they disappeared entirely. Many were hopeless and inoperable. In no instance did any tissue in the body show the least reaction after the injections nor were any systemic effects seen after large infusions. "In my opinion it is impossible not to be struck here by the remarkable selectivity of the necrotising effect upon cancer cells exerted by ascitic fluid from a recovered case of cancer, at whatever point of the body the fluid was introduced. The use of this fluid as a therapeutic measure suggests that there was some substance present, perhaps of a protein nature, that exerted an active influence upon malignant growths. The manner in which the tumor masses disappeared, by becoming degenerated and necrotic, after which they were cast off and absorbed, as the exudate was taken into the system, points to a lytic action rather than an antitoxic effect.

"I have called particular attention to these two cases because of the extraordinary importance of their implications. This effect of inflammatory exudates upon malignant cells is plainly something more than fortuitous. Lohmann (1931) has recently reported that cancer cells placed in exudates obtained from cantharides vesicles and pleural inflammations were uniformly destroyed in 6 to 14 hours, while control cells placed in normal serum remained unaffected. She thus demonstrated that cancer cells in an inflammatory environment are not capable of living on the oxygen from their fat and protein content, and that they die even when 3% oxygen is

added to the exudate for the purpose of reproducing the conditions found in vivo in the milieu of an inflammation.

"A capacity for inflammation is accordingly a requisite in the organism that is to cope successfully with cancer. This capacity is to be understood not only with reference to the degree of an inflammation but also to the sensitivity necessary for the setting up of an inflammatory condition. This sensitivity is a characteristic of the entire organism regarded as a unit, and it becomes less with increasing age. In this way we may see a reason why the body is able to restrain a tendency to proliferate in the years when it is subject most acutely to inflammations, and why proliferation meets with less opposition in the latter years of life, when inflammatory attacks, as is generally known, occur with lessened violence or not at all. The ideal prevention would then be to maintain the capacity of the organism for inflammation, so that every degenerating cell will, as soon as it forms, be in some way destroyed by obstruction, starvation or acidity. Following this line of reasoning, the role in inflammation in the spontaneous regression of cancer would be clear."

He then cited the "not infrequent retrogressions of malignant neoplasms after a sharp attack of fever, which has been reported by a number of observers. The majority of such absorptions following infections have been reported in connection with attacks of erysipelas, but instances are on record also where attacks of smallpox, pneumonia, malaria and acute tuberculosis have filled this role. In order to obtain the necessary amount of hyperpyrexia, a sustained temperature of 104°-105°F. must persist without remission for 48 to 96 hours. Injections of bacterial toxins with this end in view do not always accomplish the maintenance of such a high fever over a sufficient period of hours.

"There have been cases in which only a small bit of the tumor has been excised for purposes of biopsy, and yet high fever and subsequent regression have followed."

Finally he noted that "hemorrhages are frequently associated with regression

of tumors. It has been observed that any treatment tending to produce loss of blood has a retarding effect upon the development of neoplasms... Theilhaber observed that in the incomplete operations in which he obtained a radical cure there was always one common factor, namely, that loss of blood during operation was great, owing to the failure of the instruments to hold in the cancerous tissue. The possibility of an etiological relation between loss of blood and radical cure cannot be excluded. After extensive loss the circulation is more active, the lymph stream increases, there is greater secretion of sweat, there are more leukocytes and in a few weeks the red blood count is higher than it was before the hemorrhage - constituting conditions that serve as stimuli for resorption of retained cancer cells."

SUMMARY: 1. The human organism possesses powers of defense that enable it to resist in greater or lesser degree the development of malignant tumors.

2. These powers of defense are expressed under some conditions in the complete regression of microscopically demonstrable cancer.

3. The existence of signs of regression in biopsy sections is to be regarded as improving the prognosis in cases where complete surgical extirpation is impracticable. (DeCourcy, 1933)

The following five patients developed acute inflammation at the site of the primary or metastatic tumors:

CASE 5: Recurrent inoperable far-advanced scirrhus cancer en cuirasse, "with extensive edema of the forearm, confirmed by repeated histological examinations by Dr. Maute made during the course of the treatment with pleural exudate.

PREVIOUS HISTORY: Female, aged 37, actress. The patient had developed cancer of the right breast for which a mastectomy had been performed in January 1908, 18 months prior to consulting Dr. Theodore Tuffier of Paris, France. She was admitted to the hospital on June 21, 1909. At this time she was very thin, with a yellowish pallor, and the right arm was enormous - "a veritable elephantiasis". For two months she had been unable to move it because of the edema extending to the finger

tips. The axilla and the supraclavicular region were indurated, and there was an enormous scirrhus "cancer en cuirasse" occupying the entire right mammary region and extending from the axilla to the sternum - the entire mass was surrounded by cutaneous neoplastic nodules. The patient suffered intense pain in the arm, causing insomnia.

CONCURRENT INFLAMMATION: She had recently developed pleurisy involving the right chest and causing pain under the spine of the left scapula and rapid respiration. Tuffier believed that "if there exists a cancer antibody, the surest place to find it would be in the pleuritic effusion of a cancer patient." He felt justified in trying this out on the patient.

INJECTIONS OF PLEURAL EXUDATE: Tuffier therefore withdrew 400 cc. of the pleural exudate, cleansed it by centrifuging and injected 20 cc. of this liquid material subcutaneously every fifth day. These injections caused febrile reactions of 39°C. (102.2°F.). After the fourth injection the pleural effusion disappeared, the edema markedly diminished and the general condition of the patient was much improved.

ARTIFICIAL FEVER THERAPY: On the basis of this observation Tuffier considered himself justified in trying a more drastic technic. He therefore injected nucleinate of soda subcutaneously, determining the dose empirically at 0.75 to 1 gram so as to produce a temperature of 39.5°C. to 40°C. (103.1°F.-104°F.), and repeating the dose whenever the fever dropped to 38°C. (100.4°F.). In this way the patient was kept for three weeks in a continuous fever. At the end of this period, the edema of the arm had entirely disappeared, the pain had ceased, and the large indurated plaque had become progressively softer, leaving only a slight thickening of the skin which was not adherent to the deeper structures.

CLINICAL COURSE: Eventually the patient left the hospital apparently cured, and a year later sent word she was back on the stage. This was about three years after onset.

In reporting the case Tuffier (1910) stated: "The improvements were followed by all the students and visitors to my service, and were so marked that I might have

found it difficult to believe we were dealing with a case of cancer, if several histological examinations had not been made during the course of the treatment." He added: "This result does not surprise me, for 30 years we have known how much injections which cause febrile reactions are capable of ameliorating cancer. My master Verneuil often used to speak of this to us." Willy Meyer (1931) in reporting this case, added: "Tuffier never saw a similar result in other cancer patients that were treated in the same way."

Meyer went on to say in regard to patients developing immunity to various injected materials that "here is where the difficulty with this kind of treatment seems to be. In the experience of Tuffier as also of Bier and others, by whatever kind of injections the first strong reactions had been obtained, the system of the patient soon becomes tolerant to the injected substance, and the force of the substance is exhausted before the tumor has been healed. If now another serum or solution of some kind is employed, it may still ameliorate the cancerous condition, but less than the first one and its force will sooner become exhausted; a third still more so and eventually a change of serum will have no further effect at all.

"Postulated therefore is a serum of such range of dosage, without side-effects, that the tolerance can be overcome by increases of the injected dose, and that in this way the patient can be kept without fail and without interruption, in a long continued state of fever.

"Such a serum seems to be Coley's Fluid." (Willy Meyer, 1931, pp. 343-4)

CASE 6: Recurrent osteogenic sarcoma of lower end of the femur, confirmed by microscopic examination at Memorial Hospital and by the Bone Sarcoma Registry (Case #2065).

PREVIOUS HISTORY: A.L., male, aged 21; the patient's grandmother had cancer. The general health had always been excellent. The patient had had no serious illnesses, no operations except an appendectomy at the age of four. However, he had been subject to frequent fainting attacks for many years. About nine weeks prior to admis-

The
sion he noticed a small abrasion of dorsal surface of the right great toe, due to rubbing of his shoe. It was somewhat sore but healed gradually in a week, leaving slight redness and thickening of the skin. Onset, early in July 1934, a week after this, pain developed in the lateral aspect of the right femur in the region of the knee joint. He then first noticed stiffness of the knee joint after sitting or lying down, when any attempt at flexion or extension caused moderate pain. Three weeks after onset, the patient went to a hospital and was advised to use camphorated oil, which he did without improvement. The severity of the symptoms gradually increased and at times there was a spontaneous aching referred to the lateral aspect of the knee, which was sometimes relieved by a change of position. There was tenderness on palpation over the lateral aspect from onset, and gradually increased swelling. The skin over the joint was normal in appearance at examination at Memorial Hospital early in September 1934.

SURGERY: An incisional biopsy was performed on September 7, 1934. Amputation was advised but refused. In October 1934 an incomplete removal of the tumor was performed (wide excision) at the Hospital for Joint Diseases. By December 13, 1934, there was a definite recurrence over the antero-medial aspect of the lower end of the right femur.

RADIATION: The patient received eight x-ray treatments between December 14 and 22, 1934, given daily.

FURTHER SURGERY: A high thigh amputation was performed on February 23, 1935. The post-operative course was uneventful.

TOXIN THERAPY (Parke Davis XIII): Intramuscular injections of Coley toxins were begun March 3, 1935, and were given daily, in doses of 1 to 13 minims, without reaction. On March 10, intravenous injections were begun, the initial dose of 1/50 minim producing a temperature of 105°F. and a severe chill lasting 20 minutes. Intravenous injections were continued daily until March 25, 1935 usually producing a chill and febrile reactions of from 99.6° - 106.4°F. The maximum intravenous dose was 1/3 minim. He received a total of 5 intramuscular and 15 intravenous injections.

INFLAMMATION AND TRAUMA: In July and August 1935 he was tapped several times for pleural effusion, which was considered due to pulmonary metastases. In November he fractured his right forearm. Chest plates taken in December 1935 showed no evidence of pulmonary metastases.

CLINICAL COURSE: The stump remained in excellent condition throughout, although there was some difficulty in adjusting the artificial limb. The patient married in 1949. He remained in excellent health when last traced on December 5, 1969, 35½ years after onset. (Memorial Hospital Records; New York Cancer Research Institute Records).

In the following five cases acute inflammation occurred spontaneously at the site of the primary or the metastases:

CASE 1: Endothelioma of the left forearm, confirmed by microscopic examination after surgical removal at the Polyclinic Hospital in Philadelphia.

PREVIOUS HISTORY: Mrs. M.S., female, aged 43. The patient had always been healthy. She had had five children, four were alive and healthy, one died in infancy. The youngest child was 12 years old. Onset, in the spring of 1901, she developed a small movable painless nodule beneath the skin on the posterior aspect of the left forearm, about the junction of the upper and middle thirds. In the beginning the patient squeezed and handled it and on one occasion she drew a little blood. The mass grew steadily and painlessly for six months until it was 5 cm. in diameter. She patient was showing signs of beginning menopause.

CONCURRENT INFLAMMATION: Two weeks prior to operation the mass began to be painful and to show signs of inflammatory reaction. From that day it ceased to grow.

SURGERY: The mass was excised by Dr. Steinbach. The pathologist reported: "The mass is flattened, dense, has a smooth glistening base. On the upper surface is a portion of normal skin, which is not adherent nor in any way connected with the growth. The mass is flattened, slightly elliptical, $1\frac{1}{2} \times 2 \times \frac{3}{4}$ inches. It has a capsule, which is derived from the surrounding connective tissue. On section it presents a greyish white appearance composed of dry, friable, fibrous material... ." After staining, the following appearances were found: "The growth is surrounded with a thin connective tissue envelope which is continuous with a connective tissue stroma ramifying freely through the growth. This stroma is arranged so as to form alveoli of large size. These alveoli are filled with what appears under low power . . . to be a homogeneous degenerated substance, but which under close examination is seen to be made up of cells closely packed together, sometimes flattened so as to present a stratified appearance. These cell masses are clearly necrotic, as they do not take nuclear stain, but are stained by eosin. . . and by picric acid. . . ." Here we see the alveolus filled with medium-sized round cells, with nuclei staining

with moderate intensity. There can be no connective tissue fibres demonstrated between the cells. The cell growth is evidently derived from the endothelium of the lymph spaces. That the above cellular necrosis affects such collection of cells as those just described is shown by the fact that the stages of transition from one to the other can be demonstrated. The connective tissue stroma shows a very peculiar phenomenon: there is active hyperplasia, with a very marked round cell infiltration. New formed blood vessels are numerous. Very characteristic is the development of giant cells, which are very numerous and are uniformly applied to the margins of the necrotic cell areas, sometimes completely surrounding an alveolar space like a skirmish line. Their peripheral arrangement combined with the fact that they are so closely applied to the cell masses, and often adjust their shape to these masses (being long, slender and flattened), make one believe that their function is phagocytic."

CLINICAL COURSE: Two weeks after surgery the wound had healed by primary union. There was no evidence of recurrence six months after the operation, which was a year after onset.

COMMENT: In reporting this case before the Pathological Society of Philadelphia in April 1904, Randolph stated: "My opinion is that an endotheliomatous growth started in the subcutaneous tissue; that it grew steadily for six months, and then. . . became arrested; that a necrosis or atrophy of the cells took place; that later this inactive tissue began to act as an irritant, and the response was a productive inflammatory process which endeavored to remove a foreign mass. The very abundant presence and peculiar arrangement of the giant cells seems to show that the function of these cells is an absorptive one. I am aware that the belief that spontaneous healing of malignant growth does not occur is so strongly rooted, that it is the custom for pathologists to assume that such cases, when reported, are errors in diagnosis. I present the evidence in this case without comment, allowing the history, the record of the examination, and the drawings made from slides to furnish their own evidence." (Randolph, 1905)

CASE 2: Osteoblastic osteogenic sarcoma of the right femur, confirmed by both roentgenologic and histologic examinations, with roentgenological evidence of extensive pulmonary metastases.

PREVIOUS HISTORY: J.D., male, aged 21, of Chicago, Illinois. The family and early personal history were not recorded, except that the patient was born in Poland. Onset, in August a painful swelling developed around and above the right knee. During the next nine months the patient lost 30 pounds in weight. The pain was continuous, increased by standing and by lying in bed, leading to insomnia, but was not completely disabling as regards walking. During the three weeks prior to admission he also experienced severe sharp pains in the right ilium and back, with stabbing pain on deep inspiration. There was some cough considered to be due to excessive cigarette smoking, accompanied by "dusty colored sputum". Examination on May 7, 1929, on admission to Presbyterian Hospital in Chicago, showed a slender white male with normal findings except as follows: the abdomen was symmetrically rigid, a condition said to have been constantly present. The liver seemed slightly large to percussion but could not be palpated below the costal margin. No palpable lymph nodes were found. The Wassermann reaction was negative. The right knee was about twice the size of the left, presenting a hard, irregular, somewhat tender swelling, which seemed a part of the lower end of the femur. The blood count showed hemoglobin 80%; w.b.c. 9,200. X-ray examination revealed considerable soft part swelling with much new bone formation about the lower end of the femur, extending outward in all directions from the shaft in a radial or ray-like arrangement. The findings were typical of osteoblastic osteogenic sarcoma. A chest film May 9, 1929, was considered to be negative although a solitary dense shadow in the left hilum suggested a calcified gland or nodule or possibly a small metastasis.

SURGERY: Amputation of the upper third of the right thigh was performed by Dr. Kellogg Speed on May 10, 1929, with normal healing. The patient was discharged on June 3, 1929. (See Speed, 1943, for description of the amputated specimen and roentgenograms.)

CONCURRENT PNEUMONITIS WITH LEUKOCYTOSIS AND PULMONARY METASTASES: Examination on

March 6, 1930, 10 months after amputation showed a well-healed stump (he wore a prosthesis) but the patient had pain in the chest and expectorated bloody frothy sputum. Chest films showed numerous rounded dense shadows. A second film taken July 29, 1930 showed an increase in the number and size of these shadows. There was also present a uniform clouding of the upper lobe of the lung which was interpreted as pressure atelectasis. Subsequent films at regular intervals showed an additional number of metastases with some enlargement of the older ones. Then a resting stage occurred in which the findings varied little, the calcified character of the nammular shadows within the lungs changed little in density, outline or size. During the period from March 1930 to April 1942 the patient experienced recurrent attacks of mild dyspnea, cough, bloody sputum but no sustained loss of weight. He led a fairly active life but performed no labor. Several times he was picked up by social workers who, told of his cough and bloody sputum, insisted, under the municipal laws governing suspect infection with tuberculosis, that he report to the tuberculosis sanitarium for examination. Repeated examinations of sputa failed to reveal tubercle. There was no change of diet over that normally taken by his family. His weight varied between 129 and 138 pounds. At examination on January 19, 1942 he weighed 130 pounds, still had some chest pains and had had some hemoptysis three months previously. Skeletal x-rays were normal but chest films still showed the same scattered calcified masses. On April 10, 1942, 13½ years after onset, and at least 12 years after onset of pulmonary metastases, almost symmetrical in character in both lungs, there was no evidence of local recurrence in the stump or pelvis region. The blood findings were: R.B.C., 4,500,000; hemoglobin, 15.9 grams (99%); w.b.c., 14,100 with a differential count of neutrophiles, 2%; monocytes 4%. The serum phosphotase was 1.4 units per 100 cc., a low adult average. The patient remained well. Chest films taken on May 14, 1954 still showed multiple areas of increased density scattered throughout both lungs containing calcium and bone, but they were smaller and less dense than on previous films.

CLINICAL COURSE: On June 25, 1956 he stated that he felt better than he had for 20

years. In 1967 he reported that he was "still active to a degree. I am very short winded." In 1969 he wrote that on damp days he was subject to some chest pains and some severe pain in the stump. He still complained of dyspnea. This was 41½ years after onset of the osteogenic sarcoma of the femur with metastases to the lung.

(New York Cancer Research Institute Records)

COMMENT: This patient never had any radiation. In reporting this case, Speed stated: "The patient. . . showed little spontaneous regression of. . . metastases. . . (He) seems to have something which is holding back the fatal termination of a disease we have come to dread as possessing a high mortality." Speed tried using the blood from this patient in two cases of metastatic bone sarcoma without any apparent benefit being noted. (Speed, 1943)

His associate, Dr. Roy E. Brackin, stated in 1956 that through the years the patient showed moderate leukocytosis at those times that he visited the clinic. (New York Cancer Research Institute Records). There was no apparent reason for the leukocytosis "other than the fact that he was spitting blood at intervals".

CASE 3: Inoperable reticulum-cell sarcoma of the right supraclavicular fossa, confirmed by microscopic examination at Massachusetts Memorial Hospital, Boston, Mass. The report stated that the specimen consisted of "rapidly growing, extremely undifferentiated irregular polygonal cells, showing tremendous anaplasia and large numbers of mitotic figures. These tended to be irregularly rounded and showed a preponderance of nuclear material. The cytoplasm was extremely clear and vesicular in character, and the cells were supported by a small amount of highly vascular stroma. There were extensive areas of necrosis throughout, infiltrated with products of acute inflammation."

PREVIOUS HISTORY: R.W., female, aged 16. The family history was noncontributory. The personal history was essentially non-contributory: the patient had had the usual childhood diseases and for seven years had been taking two "pituitary" pills daily, apparently for obesity. She was admitted to Massachusetts Memorial Hospital on June 10, 1938, with a swelling in the right supraclavicular fossa of about three

months' duration (onset, early March 1938). Physical examination revealed an obese white girl with a somewhat nodular firm fixed mass of tissue almost filling the right supraclavicular fossa. X-ray studies of the right clavicle disclosed no abnormalities.

CONCURRENT INFLAMMATION: Laboratory studies showed only mild leukocytosis and a slightly elevated blood sedimentation rate. The patient was discharged with a diagnosis of chronic lymphadenitis. The mass continued to enlarge, rupturing centrally and exuding "watery material". In addition, numbness developed in the fingers of the right hand. There was no weight loss or other significant complaints. Physical examination on her second admission, 10 weeks after the first, revealed that the mass was somewhat larger and that it overlay the right clavicle. It was hard and fixed but presented centrally a fluctuant area of 4 cm. which was not warm or tender but was draining thin fluid. The surrounding skin was thickened, red and scaling. There were small hard nodes in the right axilla. No nodes were found in the left axilla or cervical regions. The hemoglobin was 11.5 gm. (74.5%); r.b.c., 4,150,000; w.b.c., 10,600, with 88% polymorphonuclear leukocytes. The blood sedimentation rate was 18.5 mm. per hour. The serologic studies were negative. Total protein was 6.54 gm. per 11 cc. with 1:1 albumin-globulin ratio. The urine was normal. A culture from the sinus in the mass showed no growth. Chest x-rays disclosed no abnormalities. X-ray of the right supraclavicular region revealed soft tissue swelling with a slight defect in the cortex along the upper border of the mid-third of the clavicle. The defect measured 7 by 1 mm. and was interpreted as possible tumor erosion. The pre-operative impression was either cellulitis with abscess or neoplasm of the lymphoblastoma type.

SURGERY: On September 8, 1938, under general anesthesia, the brauny, edematous skin overlying the right supraclavicular fossa was incised, permitting the escape of thin dark blood and revealing a 3 x 2 cm. cavity lined with friable necrotic translucent yellow-gray tissue. Several round resilient nodes about 1 cm. in diameter were palpable in the median supraclavicular area. The mass could not be ex-

cised and only biopsy was done. As stated above, the pathologist reported: "Extensive areas of necrosis throughout, infiltrated with products of acute inflammation." Because of the extremely rapid growth of the tumor, the pathologist believed it would be relatively radiosensitive.

RADIATION: X-ray therapy was then administered (200 K.V. through one supraclavicular port, 10 x 15 cm. at 5.0 cm.) a total of 1000 r being delivered. Apparently the inoperable growth regressed completely following this limited treatment.

CLINICAL COURSE: The patient remained free from recurrence or metastases 14 years after onset. In discussing prognosis in this type of tumor the authors stated: "Reticulum cell sarcoma is still a distinct problem from the standpoint of pathological classification and treatment. It is generally classified as a lymphosarcoma or as a malignant lymphoma. It is usually treated by external radiation, although for apparently inaccessible local disease surgery has some advocates. Despite a dramatic initial response to irradiation in many cases, ultimate prognosis is poor and the usual life expectancy is between 6 and 24 months from the time of diagnosis...." (Laurence & Lenson, 1952)

CASE 4: Reticulum cell sarcoma of the right tibia, confirmed by microscopic examination by Dr. Fred W. Stewart following biopsy at Memorial Hospital (V 8536).

PREVIOUS HISTORY: T.L., male, aged 37, printer, of Richmond Hill, N.Y. The family history was non-contributory. The patient had had his tonsils and adenoids removed as a child, and had pain in the shoulder and finger intermittently between the ages of 11 and 15 years. He had had no serious illnesses or operations. Onset, in February 1946 he began to notice pain and swelling in the right knee. He went to three hospitals and several doctors during the next year and was told he had Paget's disease. He was finally referred to Memorial Hospital and admitted on March 1, 1947.

HEAT THERAPY: He stated that he had difficulty sleeping, but by putting his leg on a pillow and using hot water bottles, he was occasionally able to be comfortable. However, the lesion had not prevented him from carrying on his work as a printer during the previous year. He felt that he had lost some strength. One of his physicians had put

him on a diet consisting of lean meats, no fried foods, no alcohol, and he had lost several pounds as a result. His weight on admission was 178 pounds.

INFLAMMATION AND EFFUSION: Examination on admission revealed that the right knee was swollen and perceptibly warmer than the left. There was some edema of this knee, particularly in the region of the tibial tuberosity, and this extended down the lower leg about the junction of the upper and middle thirds. On pressure there was rather acute pain, most marked on the medial portion of the upper tibia.

SURGERY AND EFFUSION: An aspiration biopsy was performed, but was not diagnostic. Thereafter there was a small effusion into the joint. An incisional biopsy was performed on March 3, 1947, under general anesthesia and reported as reticulum cell sarcoma.

RADIATION: Deep x-ray therapy was given between March 10 and 28, 1947. This was calculated as a tumor dose of 3300 r.

CLINICAL COURSE: The patient was discharged on March 22, 1947. The skin remained in good condition following radiation, but the right leg swelled periodically. By April 23, 1947, the patient had no complaints and the function of the knee joint was good. He remained in excellent condition with no evidence of disease when examined in April 1970, over 24 years after onset (Memorial Hospital Records; New York Cancer Research Institute Records).

CASE 5: Twice recurrent non-pigmented melanoma of the right ankle, confirmed by microscopic examination at the Hospital for Special Surgery following amputation.

PREVIOUS HISTORY: R.K., male, aged 21, of Manchester, Connecticut. The family and early personal history were not recorded. At the age of 15 the patient had a "cyst" removed from the right ankle. This was regarded as "probably sebaceous in nature". Onset, at the age of 19, in 1944, a growth was noted at the site of incision. There was no interference with function.

SURGERY: This growth was excised and said to be sarcoma.

CLINICAL COURSE: The following year the patient bumped his leg on a sharp corner and in January 1946 there was a recurrence.

FURTHER SURGERY: In May 1946, this recurrent tumor was excised.

CLINICAL COURSE: Recurrence again developed and between May and July 1946 the patient lost 18 pounds and felt weak and tired. He was referred to Dr. Bradley L. Coley and was admitted to the Hospital for Special Surgery on July 22, 1946. At this time there was a fungating tumor about 10 cm. in diameter on the lateral aspect of the right ankle.

CONCURRENT INFLAMMATION: There was extensive suppurative and fibrosing inflammation of the tissues surrounding the large ulcer. The femoral and inguinal lymph nodes were palpable. They were hard and about the size of marbles (see below for pathology).

FURTHER SURGERY: On July 23, 1946, Coley amputated the right leg below the knee and performed a groin dissection. Pathological findings revealed "small microscopic foci of persistent melanoma in the tissues medial and posterior to the lower part of the ulcer; extensive suppurative and fibrosing inflammation of the tissues surrounding the large ulcer; no evidence of metastatic tumor in the inguinal lymph nodes. The specimen from the right groin showed hyperplastic lymphadenitis. No evidence of tumor invasion. Chest films taken on July 24, 1946 showed punctate densities along the peribronchial markings, "not very suggestive of metastasis". The blood count showed RBC 4,900,000; WBC 9,700; Hb., 13.5 gm.; polys. 81%, lymphocytes 19%.

FURTHER INFLAMMATION: The patient developed a serosanguinous collection of fluid in the groin following operation. This apparently cleared by the time he was discharged On August 15, 1946.

CLINICAL COURSE: He obtained a prosthesis and soon returned to work. His prosthesis gave him no trouble at all. He gained a good deal of weight and by 1951 weighted 205 pounds. He then dieted under a local physician's direction and lost 10 pounds. In 1955 he obtained a new prosthesis and stated that he "got around beautifully with it". He was last traced in very good health working steadily for the State Highway Department in October 1969, having remained free from further recurrences. This was 25 years after onset. (Memorial Hospital Records; New York Cancer Research Institute Records).

The following data relate to the effects of concurrent injuries on cancer patients. It must be remembered that severe trauma, including fractures, do invoke acute inflammatory reactions, with or without fever and leukocytosis. They also stimulate fibrinolysin. (See below for the chapter on the fibrinolytic system.)

Cancer and Traumatism: Fever

Vidal (1907) in discussing the problem, stated that up to that time, in the course of the debate on cancer and trauma, one heard only of those which seemed to aggravate cancer. He drew attention to the exact opposite, traumas which ameliorate malignant tumors. He then admitted that these were quite exceptional, but he believed them nevertheless to be of great interest, as regards the study of the general laws governing the evolution of cancer.

In order to clarify the problem he distinguished between two basic types of injuries: direct trauma, immediately involving the tumor, and indirect trauma, occurring remote from the tumor in a patient with cancer.

DIRECT TRAUMA: In this group, the tumor receives a blow, a contusion more or less violent. This occurs rather often in certain localities: breast, face, etc. What are the results:

Often the tumor is very notably aggravated. These observations are well-known, as evidenced by the reports, and he cited a case personally seen: a cook, aged 48, who had for two years in her right breast a retractile, quiescent scirrhus cancer, "à marche silencieuse", without obvious axillary involvement, which caused no suffering or little anxiety. She then sustained a blow on the affected breast from a metal pot which fell from a high place, causing acute pain. The patient was hospitalized and a diffuse hematoma was found above and below the pectoral region and tending to extend into the axilla. The parts were immobilized: ice and then methodical compression were applied. Three weeks later the tumor area appeared normal, but there were vague pains in the right hypochondriac region, and ascites developed. Death occurred seven weeks after the injury, of liver metastases, verified at autopsy. There was a typical (acini-form) epithelioma, poorly developed in an area of very intense fibrous reaction.

Rarer and less easily explained are the cases of direct injuries followed by an actual regression, temporary it is true, of the injured tumor. Strange as it may seem these cases do not seem any less unequivocal. Vidal stated that in 11 years he had observed four cases of cancer of the breast and one case of epithelioma of the nose extensively invading the cheek where violent contusions produced during a certain period of time a very definite regression of the neoplasm. The growths decreased in size, the pains, if present, disappeared to the point where four patients, of which two were to be operated, all refused operation, which seemed to them more unjustified than ever. The amelioration persisted about $3\frac{1}{2}$ months, in one case $6\frac{1}{2}$ months, when the progressive enlargement then reappeared, which was arrested by surgical removal.

Vidal suggested a simple hypothesis to explain these facts. The action of the injury destroyed a large portion of the adult tumor cells by some unknown process causing necrobiosis, leaving the younger peripheral cells, which are much more resistant. From these there develops a recurrence. Moreover, experimentation seems to verify this hypothesis in a certain measure.

Vidal then reported on this experiment on a few mice, in which various forms of injury were tried. He felt the results indicated similar histological findings: diminutions, hardening, a more complete capsulation, or isolation, of the tumor.

INDIRECT TRAUMA: These are perhaps more interesting. In the previous 12 years Vidal had collected four cases in which a notable amelioration had occurred and been precisely described. Two were cases of breast cancer in women who fractured their legs. One was recurrent and inoperable, the other had not yet realized she had it, but in both the diagnosis was later proven histologically. Another was a case of fracture of the humerus in a man with an inoperable cancer of the tongue. The fourth, and much the most interesting, a case of "cerebral commotion" in an old lady who was run over by a carriage, and was suffering from an ulcerated breast cancer for which she had refused all treatment. In these four patients the effect of the concurrent indirect trauma was temporarily very remarkable. In the latter two cases, ulcerated cancer of the tongue and breast, the pain disappeared, the discharge and the hemorrhages ceased and the condition of the tongue improved so that for a month solid food could be chewed, an

impossibility for two months prior to the injury. In the breast case there was complete healing of an ulcerated area 4 cm. in diameter, with discharge en masse of a group of cancerous nodules and enormous reduction in size of the mass of axillary nodules and of the edema in the neighboring tissues. Vidal stressed the fact that this patient's accident did not injure the tumor area which was covered by a thick dressing, judging by the state of her clothes, the type of fall and the entire absence of hemorrhage at the site of an ulceration that bled very easily up to that time. The amelioration in this case lasted more than three months.

In the first two cases, of non-ulcerated growths, there was progressive increase in mobility of the tumor mass, also increased induration, as well as diminution in size, so much so that it was hoped that this formerly inoperable tumor could easily be removed. Then after five and eight weeks respectively, these two cases again showed signs of increased growth, the normal progress of the disease.

As to what to attribute the beneficial effects of the trauma in these four cases, Vidal called attention to one detail observed in all four: hyperthermia, lasting a variable time, more or less severe. In case 4, with concussion, the temperature oscillated from 39° - 40.3° C. for four days, and it is precisely in this case in which the most marked and most persistent improvement was noted. Vidal stated that this was no doubt merely a coincidence but these facts agreed with the ameliorations described following certain medical pyrexias. What is more, all the observers who for therapeutic reasons have injected cancer patients with microbes or various toxins (Fehleisen, Coley, Spronck, Répin, Doyen and Vidal himself) have obtained entirely analogous regressions, but "only at the price of a fever". He added "The constancy of this factor does not allow one to dismiss it completely."

Vidal asked by what mechanism it is invoked. If hyperthermia alone can act, it is possible sometimes that one should rather invoke the agents which induce fever.

In three cases of "closed" fractures, he believed the fever was due to resorption of the serous effusion at the site of the injury, a toxin phenomenon due to absorption.

In the case of the concussion, if the immediate hyperthermia is but the result of a nervous phenomenon, it is none the less demonstrated that there exists in the encephala-

lus hemorrhages which are completely localized and which are sometimes minute, it is true, but which will also disappear by absorption. Vidal then remembered that re-sorptions of cells or of blood serum seem, to a certain degree, to influence cancer cells (Bashford). And always, as in the experiences with toxin therapy, one is in the presence of more than one factor: the influence of hyperthermia, and the influence of toxic agents. Only experiments could determine the relationships.

It has been demonstrated that, on the one hand, the virulence and transplantability of cancer in mice is greatly reduced by heating above 37°C .

There are only two ways to produce fever in animals outside of mechanical absorption, i.e., passive fever: by heating them in an incubator or by producing a cerebral puncture in the zone of Richet with a very fine needle. As Vidal could not determine this zone very accurately in mice, he heated them in a dry heat to 41°C .

Six mice in which adenocarcinoma of the breast had been implanted 20 days previously and in which all the tumors were of approximately the same size were used for this experiment. One was kept as a control, not heated, and died on the 39th day. Two were heated to 39.5°C . daily for two hours and had a rectal temperature of 39.3°C ., dying on the 40th and 50th days. Two were heated for two hours daily at 40°C ., whose rectal temperature reached 39.9°C ., and died on the 48th and 62nd days. One heated for two hours daily at 41°C ., rectal temperature reaching 40.6°C ., died accidentally on the 83rd day. Each mouse was heated daily for a period of 18 days. In the final mouse the tumor had not increased since the 38th day.

HISTOLOGICAL EXAMINATION: The findings gave an extraordinarily striking analogy between those seen in Vidal's experience with trauma in cancer. However, the fibrous development was much less marked, while the central necrosis of the tumors was more diffuse and there was much fatty degeneration. In brief, the cellular lesions were more predominant and marked. Vidal called attention to the analogy between these findings and those described by Neelsen in the post-mortem on a case of cancer of the breast which died of erysipelas. (Neelsen, 1884).

In conclusion, Vidal stated that these observations are significant, but they are

only an isolated series, and only in cancer in mice. Such as it is, and approaching the case of concussion, where the amount of absorption was reduced to a minimum, it permits one to perceive the actual role of hyperthermia alone. In any case, Vidal believed that one could not deny its having some action, and in toxin therapy, perhaps one should assign it a role of some importance along with the special action of the toxins themselves. He then noted that the cancer cells which are killed by the toxins or fever are then absorbed and contribute consequently to an "auto-vaccination" of the patient or mouse.

"As to the necrotizing actions of toxins and poisons, these were already too well known for us to be surprised at seeing these exert a more intense effect on the central cells of a tumor which everything indicates are more fragile. But perhaps this toxic, necrotising action has been exaggerated too greatly, while neglecting the true influence of fever, which is so often inseparable from this toxic action." (We now know that pyrogens, stress and injury can stimulate fibrinolysin--see below).

Vidal added: "The value of these curious facts is at present slight, but in a matter so obscure as the etiology or evolution of cancer, it is important for the biologist and the surgeon to penetrate the mechanism of the modifications which cancer may undergo. For it is perhaps the exception which can best demonstrate the rule and teach us finally what exact laws govern the development of a malignant tumor." (Vidal, 1907).

following

In the following case there was concurrent fever and leukocytosis ~~plus~~ confinement.

DIAGNOSIS: Reticulum cell sarcoma of the left sixth rib with multiple metastases to both breasts, the right ilium, and the right wing of the sacrum, the pelvis and upper femora, confirmed by microscopic examination by Dr. Fred W. Stewart at Memorial Hospital, (N. 170) on July 12, 1954, and by x-ray examinations (originally the case had been reported by Stewart as "primary inoperable carcinoma of both breasts with metastases to the spine, pelvis and ribs, in exceedingly malignant form").

PREVIOUS HISTORY: Mrs. M.B., female, aged 28, of Staten Island, New York. The family history was negative for cancer, tuberculosis or diabetes. The patient had had the usual childhood diseases, no operations and no illnesses other than an occasional cold and headaches. The patient became pregnant in November 1939. Onset, in May 1940, three weeks before delivery of twins, she began to lose weight, felt weak and had diffuse aches and pains in the back and lower abdomen. These symptoms were attributed to the pregnancy. At the same time a painful lump was noted in the left breast. Following delivery of living twins the patient had much pain in the back, abdomen and pelvis.

FEVER: She ran a temperature, ate poorly, did not nurse her babies and lost weight.

CLINICAL COURSE: The lump over the left anterior chest wall ceased to pain her but was swollen. During the two weeks prior to July 22, 1940, the patient had very severe, sharp, sudden pinching pains starting in the hip region and spreading down to the knees especially on the right side. These attacks gradually eased up after 30 minutes, the pain persisting as a dull ache. These ceased to occur a few days prior to admission to Memorial Hospital. The patient did not walk much because this caused pain in the hip region and her legs were weak. X-ray examinations taken after confinement were said to have shown a "soft tumor over the left anterior ribs". Examination on admission to Memorial Hospital, July 20, 1940, revealed an oval tumor 4 cm. long and 2.5 cm. high in the left sixth rib in the mid-clavicular to outer clavicular line. This was smooth, very firm, non-tender, not attached to the other ribs nor to the overlying skin. These were several discrete, firm, round, freely movable nodules about 1 cm.

in diameter in both breasts and several moderately soft rounded non-tender nodes in both axillae and both inguinal regions (more numerous in the left axilla).

SURGERY: An aspiration biopsy of the lesion in the left sixth rib was performed on July 23, 1940, and the next day under general anesthesia an incisional biopsy was performed of the lesion in the rib and one of the nodules was excised from the right breast.

FEVER AND TRANSFUSIONS: A transfusion of 520 cc. of citrated blood and 500 cc. of normal saline was given that day. The patient's temperature rose to 102.4° F. the day after operation and to 102.6° F. the second post-operative day. It reached 101.8° F. on July 27 and 102° on July 28, 1940. Thereafter there was only about one degree or less. She was given a second transfusion, 500 cc. of blood by the indirect method, on August 5, 1940. On August 4, 1940, the temperature reached 102.2° F. Thereafter it remained normal or subnormal (97°-98.9°). Dr. Howard C. Taylor, Jr., examined the patient on August 2, 1940, and reported that both breasts contained 10 to 20 freely movable nodules each 0.5 to 1.0 cm. in diameter. He commented that it was unusual for them to be completely movable. The axillae contained small nodes and there were no definite supra-clavicular nodes. One subcutaneous nodule 2 cm. in diameter was present in the epigastrium. There was no liver enlargement. He regarded it as probably carcinoma of the breast but asked if the adrenals had been considered. X-ray examination on July 16, 1940 (prior to admission) had revealed a sharply defined area of destruction in the right wing of the sacrum, similar in appearance to the area present in the left sixth rib. Submitted films of the chest were reported by Dr. Ralph Herendeen as revealing a rounded, faint area of increased density in the plane of the left mid-lower lung field, and a small semi-lunar shadow of increased density along the lower left lateral chest. The adjacent ribs (sixth and eighth) revealed destruction. Films of the lumbar vertebrae and bony pelvis revealed suggestive bone changes in the inferior portion of the right ilium.

RADIATION: Deep x-ray therapy was given to the pelvis through anterior and posterior right and left ports totalling 1,200 r to each of these areas, delivered between

July 26 and August 9, 1940. Between July 30 and August 6, 1940, the left sixth rib anteriorly received 2,100 r in 300 r doses. Between August 9 and 17, 1940, the left and right breast each received 1,600 r, in 200 r doses.

CLINICAL COURSE: X-ray examination on September 5, 1940, revealed evidence of metastases throughout the pelvis and in the upper femora but there was no destruction seen in the lumbar vertebra. Chest films revealed evidence suggesting some bone regeneration in the anterior end of the left sixth rib. Another area was seen in the eighth rib posteriorly near the posterior axillary line. The patient was discharged on August 17, 1940, slightly improved. Her chief complaint during the last week was weakness. Dr. Bradley L. Coley noted on September 18, 1940, that "There certainly has been remarkable improvement in this case from almost every angle." A week later he reported: "The breasts, bone, rib areas are not causing symptoms and no palpable disease is evident, yet the general condition does not seem quite so good...and there has been a little weight loss." Her weight in November 1940 was 102.5 pounds. Blood counts showed the hemoglobin had gone down nine points in the previous week. The white blood cells remained 6,200. (Later blood counts showed that the w.b.c. rose to 8,000 in January 1941 and in April 1941 was 7,200. In June 1941 it was 5,650.) She was given Lextron (Lilly) and told to take two tablets a day.

THIRD TRANSFUSION: A third transfusion was given on October 10, 1940, of 500 cc. citrated whole blood. It caused no reaction.

CLINICAL COURSE: Her general condition remained satisfactory. X-ray examination on February 21, 1941, revealed slight reparative changes had occurred in the previous four or five months, particularly at the lower portion of the left sacro-iliac joint, the left acetabulum, and the right mid-ilium. Slight similar changes were present in the neck of the femur. Minor improvement continued to be evident in several small areas as seen in films taken October 3, 1941, but the changes were not significant. The radiation given to the pelvis caused radiation menopause. In August 1941 she complained of having 15 or 20 hot flashes a day and several at night, also great nervousness, irritability and marked lassitude. On August 27, 1941, Coley noted that the tumors present in the breast and ribs had completely disappeared. Estrogenic

hormones were given (Progynon B), totalling 18 injections ending October 4, 1941. These reduced the flashes to one or two mild ones a day. They returned in full force on October 27, 1941. Stilbestrol was then tried (0.1 mg. daily increased after three days to 0.2, 0.3, and finally to 0.5 mg. daily.) This was continued during January and at that time it was noted that she had an occasional sticking pain in the left sixth rib and occasional slight pain in the breasts. When stilbestrol was stopped the flashes returned. Films taken November 2, 1942, revealed the presence of a compression deformity in the body of the eighth dorsal vertebra. Films of the pelvis revealed practically no changes in the area of metastases in each ilium. There was suggestive, but no definite, evidence of involvement of the neck of each femur. Films taken July 22, 1943 revealed evidence of further bone regeneration and no evidence of lung metastases. In March 1945 the patient stated that the hot flashes were well controlled with premarin, but that insomnia was very troublesome. Vitamin B complex was given. On October 31, 1945, films of the lower ribs revealed a fracture deformity of the posterolateral portion of the left eighth rib with some productive changes, the appearance being consistent with a pathological fracture. Clinically Coley reported that the patient was "free from any evidence of disease in the breasts, chest or elsewhere." At examination on January 27, 1947, Coley reported: "Negative findings for any pathology in the breast and no evidence of disease in the rib or spine at the site of previous metastatic cancer. Her general health is good....This is a paradoxical case whose survival for 7½ years I can hardly account for." In 1950 Coley reported that the patient was "in excellent health 10 years after a highly malignant tumor with involvement of spine and ribs and both breasts....We have no case in our experience that begins to approach this one." In 1956 the patient had infectious mononucleosis. In 1959 severe virus pneumonia required hospitalization. She remained in good health in 1970, almost 30 years after onset, with no evidence of disease. (Memorial Hospital records; New York Cancer Research Institute Records.)

The following two cases had cutaneous inflammatory episodes and fever.

DIAGNOSIS: "Fully malignant osteogenic sarcoma of the right femur", confirmed by microscopic examination by Dr. Fred W. Stewart following amputation. The gross description: "In the posterior aspect and medial portion of the knee joint a definite swelling can be seen. Dissection of the limb reveals a definite edema of the soft parts, especially the muscles. Further dissection reveals that the tumor is located mainly posteriorly but surrounds the whole lower end of the femur. The periosteum is elevated and perforated by the tumor and there is minimal extension of the tumor to the adjacent muscles. Cut section of the femur reveals the tumor to measure 5 x 8 cm. It also confirms that it entirely surrounds the lower end of the shaft of the femur. The lowest portion of the shaft has been destroyed, but the rest of it up to 5 cm. is fairly intact. The tumor itself has an irregular surface, is moderately firm in consistency, somewhat necrotic with yellowish pink-white color. There is no other extension to adjacent soft parts except the above mentioned minimal extension to muscle. The knee joint appears intact. The tibia and fibula grossly normal." (Q 7175)

PREVIOUS HISTORY: A.L., Jewish male, aged 10, born in Holland and living in Brooklyn, N.Y. The child's grandfather had tuberculosis, and uncle, an aunt and a grandmother had died of cancer. There was no family history of asthma or hay fever. The child had had measles, chicken pox and pertussis, none of them severe cases. His tonsils and adenoids were removed at the age of eight. He had always been a small child of asthenic and hyperirritable type. Onset, On July 15, 1943 he first complained of moderate pain in the right knee and lower femur. The pain persisted and a week later the patient was taken to a doctor and bed rest was advised. X-ray examination on August 8, 1943, revealed no abnormalities. By August 15, 1943, the pain in the femur had become somewhat more severe and a definite swelling developed in the right lower femur. The parents consulted a pediatrician, Dr. Hans Behrendt, who found marked local swelling, tenderness and pain with extension. There was some fluid as evidenced by a floating patella. All blood studies were negative. X-rays showed some bone changes which were more apparent in a film taken on August 13, 1943. At this time the child had a temperature of 100⁰F. Behrendt regarded the condition as a bone tumor and referred the case to Dr. Walker E. Swift. An aspiration biopsy was performed and the condition was reported as osteogenic sarcoma.

RADIATION: X-ray therapy was administered for three weeks beginning on August 19, 1943 (180 K.V., four portals, each receiving 1, 125 r in 150 r doses, two portals daily). The tumor dose was calculated as 3,600 r. Although there was some relief of pain during the second week of radiation, pain returned in the third week and the

child became very ill, vomiting practically everything during the first week of September.

CLINICAL COURSE: As Swift was away, the parents consulted Dr. George Pack. Since the tumor had not responded to radiation, amputation was advised. Examination on admission to Memorial Hospital on September 9, 1943, revealed a somewhat timid child who appeared pale and weak. The right knee was very markedly swollen and there was a soft mass protruding into the popliteal space. The knee was partly flexed and ankylosed. Examination of submitted films revealed what was apparently an osteogenic sarcoma of the lower end of the femur, apparently well localized as far as the medullary part of the bone was concerned, but it did involve the soft tissues surrounding the bone. The child had lost a considerable amount of weight and was anemic and in poor general health.

CONCURRENT INFLAMMATION: It was noted on admission that he had an erythema multiforme of the hands, arms and legs, and that the temperature was 101°F. During his hospitalization the temperature ranged between 99°F. and 101.8°F. Several enlarged nodes up to 1½ cm. in diameter were present in the right groin at this time, but these were regarded as apparently inflammatory. The tumor area was distinctly hot, and the skin showed evidence of radiation reaction.

SURGERY: A mid-thigh amputation was performed by Pack on September 11, 1943. Pathological examination of the specimen, as noted above, revealed that the tumor was somewhat necrotic, with definite edema of the soft tissues.

POST-OPERATIVE FEVER: There was some fever for five days. The temperature approached normal on September 16 and the child began eating better. He was discharged on September 18, 1943.

CLINICAL COURSE: He remained free from recurrence or metastases. Pack noted on May 16, 1950, that he had developed bilateral gynecomastia, but without secretion from the nipples. He remained well and free from disease when last traced in 1959, 16 years after onset. (Memorial Hospital Records)

F. W. Stewart briefly cited a case treated by Pack, prior to 1944: an inoperable myosarcoma uterus in an adult, ^{after} At exploratory operation the condition was considered hopeless as the tumor had spread through the whole pelvis and in the mesenteries. It was soft, very vascular and hemorrhagic. It was biopsied and the radium bomb was administered with no evidence of radiosensitivity, i.e. the mass failed to regress at all. Just before completion of treatment and within almost a matter of hours, a dramatic change occurred: the patient developed a high fever, urticarial rash, high eosinophilia, and within a few days lost kilos of tumor and ascitic fluid. The tumor entirely disappeared. About five years later, some insignificant lesion showed a hypersensitive reaction. She was alive and free from disease 10 years after regression under fever and intense inflammatory reaction. (F. W. Stewart, 1952)

Allen and Spitz (1953) called attention to the varying stromal reaction seen surrounding a junctional nevus and a juvenile melanoma as compared with malignant melanoma. They stated: "Rarely is an activated junctional nevus free of a zone of inflammatory cells, which are usually lymphocytes along with some histocytes and eosinophilic leukocytes - disposed in the upper cutis; so as to resemble somewhat the inflammatory pattern of lichen planus. Although this reaction is the usual feature beneath the activated junctional nevi, the juvenile melanomas and the superficial melanocarcinomas, it is often inconspicuous or absent at the advancing margins of the more deeply infiltrating melanocarcinomas, as if the defensive barrier of the inflammatory cells had been broken through."

The authors noted that even a very superficial dermal invasion of melanocarcinoma is already associated with distant metastases in a relatively large number of cases, in contrast, for example, with an analogous tumor, the squamous cell carcinoma. . .The malignant junctional cells have easy access to the lymphatic and venous channels immediately beneath the epithelium as they drop off from the epidermis and penetrate their thin walls to enter their waiting, gaping lumina. The cells of the squamous cell carcinoma have similar opportunities that, however, are often balked because of the far greater cohesiveness as a rule, of the cells of the squamous cell carcinoma in contrast with the striking and characteristic lack of cohesiveness of the cells of superficial portions of the melanocarcinoma, especially while they are still in the junctional stage."

Pregnancy and Malignant Melanoma:

"It has come to be adopted as fact that pregnancy aggravates the prognosis of many cancers, particularly that of mammary carcinomas. There seems to be no reason to doubt this general thesis, especially as it concerns the apparently increased aggressiveness of breast cancers during gestation. However, the actual documentation with regard to the malignant melanomas appears to us not altogether supportable with the data now available. . .or from the literature." If pregnancy does actually accelerate the growth and metastasis of melanocarcinoma, this hypothesis, while it

may well be true, remains to be proved.

If the report that ACTH and cortisone may produce junctional nevi is substantiated, an important lead may be forthcoming. Inasmuch as the level of ACTH increases in pregnancy, the possibility of its action in the production of junctional nevi, which, in some cases then go on to melanocarcinoma, must be carefully evaluated.

Similar data are desirable (and lacking) with regard to the effects of disturbances of gonads and other endocrine organs on the initiation, activation and perhaps retardation of junctional nevi in both children and adults.

Significance of Five Year Survivals:

Twenty-three per cent of 500 patients who died succumbed to their disease in less than a year. Thirteen per cent died of their metastases five or more years after their diagnoses: 11% of these survived five to ten years and 2%, 11 to 24 years.

Allen and Spitz used the term five-year survival to those cases clinically quite free of tumor at the five year mark and thereafter.

Sex Incidence:

While the incidence is about identical in males and females, 38.8% of women survived, while only 18.2% of men survived five years, an impressively significant difference.

Therapy:

As a general rule local adequate excision of the primary tumor with dissection of the regional lymph nodes is the method of choice. . . In none of the 123 survivals of the determinate series was radical amputation performed. In only three of these was a mid-thigh amputation performed, in each for a primary tumor of the heel. In two of these patients there had been local recurrences prior to amputation; in only one of these instances had a node dissection been done in addition to the amputation. A relatively high percent of patients, 68.3%, who survived five years or more, were treated by local excision of their primary tumors.

They concluded that the high mortality from malignant melanoma with whatever therapy, combined with the seriousness of the loss of extremity, as well as the hope that a given case will fall into the group cured by merely local therapy, all tend to discourage the use of this radical approach. (Allen and Spitz, 1953)

Gowans and McGregor (1965) have reviewed the immunological activities of lymphocytes. The wealth of experimental detail has catapulted the lymphocyte into prominence as the cell type intimately engaged in delayed hypersensitivity. They stated: "The immunological responses of an animal are put into effect by the activity of the fixed and circulating cells which, in aggregate, make up its lymphoid tissue... The small lymphocytes are the predominant cell-type in normal lymphoid tissue and the predominant lymphoid cells in normal blood. Small lymphocytes can interact with foreign antigens in the host and initiate an immune response against them...Lymphocytes which enter the blood of specifically sensitized animals can destroy cultures of target cells after making physical contact with them...The presence of specific antibody in small lymphocytes, their long life span, and their ability to respond in vitro to specific antigens when the donor is an appropriately sensitized human subject make it worth considering that small lymphocytes may be the carriers of long-term immunological memory." These authors give 297 references in this review.

Delayed hypersensitivity, unlike systemic anaphylaxis, does not depend upon detectable humoral antibodies, but rather on an immunologically specific inflammatory response. Unlike non-specific inflammation invoked for example by turpentine or xylene, it has a distinct induction period and a high degree of specificity...Its prototype is the tuberculin reaction and this has been shown to be quite susceptible to suppression by alkylating agents or antimetabolites."

Willoughby and Spector (1964) noted that lymph node cells sensitized with tuberculin yielded a permeability factor which strikingly increased vascular permeability to circulating protein-bound azo dyes in the skin of rats, guinea pigs, mice and rabbits. This factor is present in presumably immunologically competent cells, can bring about appropriate vascular and cellular changes and is demonstrable in increasing concentrations during the development of the reaction and in falling concentrations as the reaction diminishes. The lymph node permeability factor may ultimately be resolved into a group of substances responsible for permeability changes, leukocyte emigration and fibrinoid formation. It may act as a mediator of inflammatory reactions due to delayed hypersensitivity.

Southam (1968) stated: "It is firmly established that many cancer patients have impaired immune responses. Iatrogenic immunosuppression contributes to this impairment in many patients, but the data indicate that there is also impairment which is related to the neoplastic disease per se. The defect appears to be in responses requiring the mediation of cells, rather than in those which are dependent upon the production and reaction of serum antibodies. The immunologic deficiency is most frequent and most severe in patients with widespread and debilitating cancer but it is not a consequence of debility alone."

Delayed hypersensitivity reactions of patients with lymphomas or nonlymphomatous cancer have been studied by several investigators including Southam using tuberculin and other microbial antigens. Solowey and Rapaport (1965) used five microbial antigens of which streptokinase and streptodornase gave the most positive reactions. They found 73% of the cancer patients were anergic to this antigen preparation.

T.H.M. Stewart (1968-69), in studying delayed hypersensitivity reactions in cancer patients stated that "A correlation has been made between the degree of stromal infiltration of a tumor by lymphocytes and the presence of a delayed hypersensitivity reaction in a patient toward cellular extracts of his own tumor injected intradermally.

A literature review suggested that patients with such lymphocytic infiltration have a good prognosis. The relative inefficiency of such a cellular defense mechanism in cancer patients was apparent. In the light of our present knowledge of lymphocytic destruction of target cells, Stewart proposed that non-specific antigenic stimuli may improve such a defense mechanism. "Evidence in support of this is taken from experimental animal systems and the history of medicine, and, in particular, from the work of Dr. William B. Coley (Stewart, 1969).

Stewart induced regression of an inflammatory skin lesion (mycosis fungoides?) by intradermal injections of varidase (non-toxic enzymes derived from hemolytic streptococci). He stated that the resemblance of the ensuing delayed reaction to a small area of erysipelas was very marked and added: "This phenomenon closely resembled the early clinical trials of Coley who used extracts of hemolytic streptococci in inducing regressions of sarcoma." (Coley, 1891, 1893)

Ratner, et al (1968) produced alterations of lesions of mycosis fungoides by direct imposition of delayed hypersensitivity reactions, i.e., complete or partial clearing of the lesions lasting several months in 22 of 31 treated plaques.

MacCormac (1933, 1934) reported two cases of mycosis fungoides markedly benefited by erysipelas accidentally contracted: one patient was gravely ill (apparently about to die), when the infection occurred. The lesions disappeared dramatically and the disease remained quiescent and stationary for 15 years, except for a few lesions. The other case was in the tumor stage with ulcerated lesions when erysipelas developed. Some of the tumors disappeared, others flattened and were no longer tumefied. Klauder (1936) treated mycosis fungoides by malaria inoculations and reviewed the literature.

Wills and Hadfield (1925) used Escherichia coli vaccines in treating such a case and reported that by the fifth injection the mycotic lesions had disappeared. The patient remained free from eruptions for 7½ months, then relapsed.

Gross (1965) found that patients with terminal cancer showed a nearly complete absence of delayed hypersensitivity response. A small number of patients cured from cancer for five or more years showed a significant DHR. Patients more recently surgically treated for cancer showed a variable response. He suggested that the delayed hypersensitivity response is an expression of a non-specific immunological mechanism which may have a protective or therapeutic significance. He added that whether it can be induced by various antigens has to be further investigated.

Waldorf, et al (1968) and others have noted that in an aging population the ability to develop delayed hypersensitivity is impaired. They obtained alterations of lesions of mycosis fungoides by direct imposition of delayed hypersensitivity reactions.

Hughes and Lytton (1964) stated: "It would be reasonable to attempt to stimulate the antibody response in patients with early malignant lesions before their immunological responses become depressed, particularly if they exhibit evidence of delayed cutaneous hypersensitivity to extracts of their own tumors. Perhaps this is related to the suggestion of Crile (1950) that it is wrong to remove unaffected regional

lymph nodes in early carcinoma of the breast, as this may interfere with the host-defense mechanism, for the removal of the regional lymph nodes has been shown to delay the rejection of a skin homograft."

A great many investigators have noted that in advanced cancer there is a true depression of lymphocytic activity, or the ability to develop delayed hypersensitivity reactions (Waldorf, 1968) and other factors involved in immunologic responsiveness to cancer. We must learn how to stimulate these defenses more effectively even in older patients.

It is significant that in individuals or populations whose immunologic responsiveness has been maintained at a higher level, due to a greater incidence of endemic infections or infectious diseases, the incidence of cancer is significantly lower. R.L. Smith, (1956, 1957) reported on this as regards the American Indians compared with the white population.

Recently several investigators have reported that children in Africa with Burkitt's lymphoma or leukemia have long term remissions amounting to cure following only one or two doses of chemotherapy. (Burkitt, 1965 and 1967).

Rall (1968) reported on the importance of dose scheduling to maximise tumor damage and minimize host damage in the treatment of Burkitt's lymphoma and leukemia. He noted: "Many of the African patients with Burkitt's tumor have a very active bone marrow due to previous malaria or other infections. Perhaps the hyperstimulated bone marrow, in which there are more cells than are in quiescent bone marrow, is more resistant to alkylating agents.

Brew (1967) and David and Burkitt (1968) reported on long term remissions in four out of eight unselected patients with Burkitt's lymphoma following seemingly non-specific treatment with Septicemine (which contains Hexamine iodomethylate 6.3 g., hexamine, 1 g., sodium benzoate, 1 g., saccharose 5 g., distilled water 100 ml.).

Burkitt and Kyalwazi (1967) discussed spontaneous regression of African lymphoma: This evidence of spontaneous remission adds to the evidence provided by long term survivals following single dose chemotherapy that the host tissues can exert a strong anti-tumor response against this tumor. This lends encouragement to the whole concept of treating cancer by attempting to enhance the patients own resistance to the neoplastic cell."

Burchenal (1966) also believed that the long term remissions seen in Burkitt's tumor are probably the result of a combination of chemotherapy and host defenses and he suggested that "such a bilateral approach would seem essential in acute leukemia."

Klein et al (1968), in a paper on host defense and Burkitt lymphoma stated, "In experimental systems the same population of leukemia cells that produces generalized disease in animals whose immune response is weak or absent may grow as more localized solid tumors in partially resistant hosts. It is therefore quite conceivable that some neoplastic diseases of the lymphatic system, occurring outside the geographic regions where Burkitt's lymphoma is endemic, may be due to the same agent but may show different localization and growth characteristics as a result of the differences in the host's immune status. Immunologic approaches may be reflected by cross-reacting antigens.

In this connection one may consider the spontaneous regressions and the excellent responses seen in the treatment of metastatic choriocarcinoma, for this tumor arising from the trophoblast of the placenta is more foreign to the host than most types of malignant tumors. Bagshawe (1962) stated that these specific immune mechanisms may account for the high rate of response to chemotherapy (66%) in these patients.

Silk reported (1967) that the plasma from patients with carcinoma appears to be able to inhibit in vitro lymphocyte transformation. He suggested that this may be one of the factors responsible for the anergy that occurs in cancer patients. Clinically and experimentally there is a suppression of immune responsiveness associated with tumors.

Aschoff (1924) first used the term reticulo-endothelial system as a collective name for a system of cells distributed throughout the body and especially demonstrated by the use of vital stains. These include the reticular tissue in general and the phagocytic cells of the spleen pulp, bone marrow, lymph nodes and especially the Kupffer cells of the liver.

Jaffe (1927) noted that there is an alteration of the entire reticulo-endothelial system during gestation. He quoted Lundwall as having observed a more rapid storage of Congo red by the RES in pregnant than in non-pregnant women. Hoffbauer, confirming the earlier observations of Hornung, found that during pregnancy a phagocytic tissue develops in the broad ligaments which is most extensive after prolonged labor. He points out the great importance of the local accumulation of macrophages for resistance against infections. The macrophages develop from the adventitial cells.

Stephan (1926) regarded the RES as the most important defense mechanism against malignant tumors. Jaffe noted that in leukemia it has been repeatedly shown that antibody formation is diminished. Piney has called Hodgkin's disease a reticulo-endotheliosis. Neudorfer suggested that the reticulo-endothelial cells are important in preventing metastases. Erdmann showed that blocking these cells with India ink makes possible the transplantation of tumor cells or tumor filtrates. Other investigators have confirmed this.

Jaffe found that in patients where there was an intensive new formation and desquamation of the endothelial cells, metastases were usually absent, but that when the endothelium shows no reaction there were metastases. Jaffe suggested that the proliferation of the endothelium is a defense reaction against tumor cells carried to the lymph nodes by the blood stream.

The work of Ludford (1929-1934), Bruda (1929), Zacherl (1930), Braunstein (1931) and Foulds (1932), as well as more recent studies by Molomut et al, (1952), Toolan (1949-1955), and Heller (1953-1955) all suggest that natural or induced immunity to neoplasia may be weakened or destroyed when the reticulo-endothelial system is blockaded or its activity decreased.

The question has been raised as to whether it would be possible to produce increased resistance to cancer by stimulating the activity of the RES by proper dosages of x-ray, or by injections of some vital dye or by bacterial toxin injections.

The effects of roentgen ray irradiation upon reticulo-endothelial activity has been the subject of intensive investigation by many authors, including Murphy and his group (1913-1926) and Mottram and Russ cited above in the section on lymphoid activity as it relates to tumor immunity. It has been established that the RES is very sensitive to radiation, the post-radiation effect depending entirely upon the dose applied: a small dose stimulates, increasing the protective properties, while a larger dose inhibits or destroys the defense mechanisms of the RES, either against infection or malignancy. Maximum resistance following small doses seems to be reached three to four weeks after irradiation.

Arons and Sokoloff (1939) stated that they were convinced that malignant disease, even in its earliest stage, is not merely a local disease, but rather a general disturbance of cellular dynamics. They believed that we cannot neglect the possible effect of local irradiation upon the general health and upon the reticulo-endothelial system in particular, because the resistance to malignancy and to metastases depends to a great extent upon the healthy state of the RES and upon its ability to react.

The state of overactivity of the RES associated with lymphocytosis seems to be unfavorable to tumor growth. According to Sokoloff, the immunity against tumor depends upon histiocyte reaction, which may be observed in different organs of the animal. When the macrophagic reaction is more intense and of longer duration, the resistance to tumor growth seems to be more pronounced.

Volterra (1932-1935) also believed that there is a direct relation between tumor immunity and the state of the RES. In his opinion the substances Caspari (1929) called necrohormones produced by tumor cells are disposed of by histiocytes, and if the quantity of this necrotic tumor tissue is too large, a paralysis of histiocyte activity occurs and immunity is lessened.

Thus the experiments of Caspari (1922), Bruda (1929), Ludford (1929), Mottram and Russ (1919) and others indicate that if the RES is depressed by heavy radiation, or

blocked by massive doses of vital electro-negative dyes, the resistance to transplantable tumors can be broken down almost completely. (Small doses of each of these agents have a stimulating effect, massive doses a depressing effect.)

In all probability there exists a number of other substances which, according to the quantity applied may act as stimulants or depressives of the RES, and therefore, as inhibitors or stimulants of tumor growth. This fact may be of great importance, and may explain some of the conflicting reports in the literature. (Arons and Sokoloff, 1939)

Stern (1941) discussed certain aspects of the relationship between malignant tumors and the reticulo-endothelial system. He stated that on the basis of numerous reports published 1931-1941, as well as his own investigations with Willhelm, he was able to demonstrate that the morphologic and functional status of the reticulo-endothelial system is intimately connected with the tumor process and that alterations of the RES by suitable experimental factors had a marked influence on tumor development and growth.

Structural and Functional Changes: He cited (a) the fact that atrophy or insufficiency of the reticulo-endothelial elements were found in patients who had died of cancer or in animals with experimental tumors. (b) that a hypertrophic reaction of the RES occurs shortly after tumor implantation in animals. "This hypertrophic stage has been said to persist even if the animal is resistant to the inoculation and tumor growth does not appear, which fact seems extraordinarily important for the conception of a close relationship between the function of the RES and tumor development. Where tumor development and progressive growth occur, however, the hypertrophy of the RES is replaced by marked atrophy.

Stern noted that benzopyrene, tar and x-rays all cause marked damage to the RES prior to the appearance of their carcinogenic activity. He pointed out that one peculiarity of carcinogenic stimuli: "The same stimulus possesses carcinogenic and cancer curative qualities. For a long time this has been well known as regards x-ray, and radioactive substances, but the same is true of arsenic and carcinogenic hydrocarbons.

This dual action depends on dosage; while weak stimuli inhibit cancer, strong ones produce malignancy."..."It is extremely tempting to consider the RES as responsible for this, for we know that this system is activated by comparatively weak stimuli and paralyzed by strong ones."

Stern stated that further extensive research is required, including a study of the RES in animals with a very high percentage of hereditary spontaneous cancer. He also suggested that a deeper insight into the pathology of cancer patients would be gained by injecting them with harmless colloids antemortem, as was done by Eppinger (1922) for other purposes, and thus render possible a more exact postmortem histologic study of the RES.

He then discussed possible diagnostic tests based on the functional analyses of the RES. (Congo red test of Adler and Reimann).. However, he stated that the detection of damaged RES function could not be considered as a measure of cancer diagnosis because an impairment of this system occurs under various other pathologic conditions and is therefore not specific.

(1941)

Stern tested 100 patients with microscopically proven cancer in a New York City hospital with the Congo red test, and as controls he tested 49 patients clinically free from malignancy. In 86% of the cancer patients a distinct, usually severe disturbance of the RES was found. Stern concluded that the degree of reticulo-endothelial damage permits a prognostic evaluation, and the repeatedly performed test during and after treatments allows some estimate of the therapeutic effect.

Kageyama (1937) reported a decreased reticulo-endothelial function in rabbits with Kato sarcoma and analogous results were obtained by Stern in rabbits with Brown-Pearce carcinoma. Stern regarded the studies of Sato, Wetzler-Ligetl and Weisner as particularly important. They applied the modified Congo red test to rabbits treated repeatedly for several months with a carcinogen (1-2-5-6-dibenzanthracene) and found that this carcinogen produced distinct lowering of the reticulo-endothelial activity in 13 out of 14 animals.

All these studies are based on the fact of the essential colloid-storing ability of the RES. In recent years, numerous authors have established interesting correla-

tions between the RES and other biologic processes. While the important role of the RES in immuno-biologic phenomena has been known for a long time, these studies revealed the significant share of the RES in lipid and carbohydrate metabolism and in oxydative processes generally. Furthermore, phenomena of physical chemistry and of vitamin assimilation (especially vitamin A) have been shown to be connected with RES function.

Stern then discussed the relation of the carcinolytic phenomenon to the RES. This phenomenon discovered by Freund and Kaminer in 1910, was defined by them "as the fact that sera of cancer-free persons are able to dissolve a certain percentage of cancer cells in vitro...whereas sera of cancer patients not only lack this quality, but even protect cancer cells from dissolution by 'normal' sera." They claimed the presence of a carcinolytic factor in normal serum, and the presence of a "cancer cell protecting factor" in the cancer serum.

Stern then studied the problem. He found that effective damage of the RES by splenectomy or blockade (due to India ink, trypan blue or carmine) in normal tumor-free animals caused a change in their serum, so that it exhibited the characteristic features of a "cancer serum", i.e., it was unable to dissolve cancer cells and protected them from dissolution by normal serum. However, if sera exhibiting the cancer cell-protecting-ability were treated in vitro with organs of the RES, this quality was destroyed, and it behaved as normal serum.

Stern concluded that it is a function and characteristic of the RES to prevent the formation of the cancer protecting factor in the normal organism and that the occurrence of this factor in the body fluids is caused by an insufficiency of the RES. Thus, also the characteristic behavior of cancer patients in the lack of carcinolytic reaction may be considered as the indication of a damaged RES.

Kageyama (1937) showed that the experimental damage of the RES in animals caused a shift in the pH of the blood toward the alkaline. (This same change occurs in the blood of individuals with cancer.)

Stern concluded that the functional analysis of the RES carried out by various methods suggests a damage of this system in malignant conditions. He urged that further studies be made which might yield important new viewpoints concerning the etiology

and treatment of malignancy.

Significance for Therapy: The evidence of a close relationship existing between the RES and tumor pathology has incited several investigators to attempt therapeutic applications. These studies were further supported by the fact that many investigations using animal experiments had demonstrated acceleration of tumor development and tumor growth following experimentally produced injuries to the RES (splenectomy, or excessive blockade with colloids such as trypan blue, carmine, India ink, etc.). These observations were made on transplanted as well as chemically produced neoplasms. (Andervont, 1936)

Stern stated: "If, therefore, the artificially produced depression of reticulo-endothelial activity must be considered as a tumor-favoring condition, it seems justifiable to assume that...an experimental stimulation of that system might have an antagonistic, therapeutically useful effect on neoplasms." He classified such attempts as follows: (a) Efforts to isolate from the reticulo-endothelial organs, factors or fractions which could vicariously complement a decreased reticulo-endothelial function i.e., a substitution therapy in the hormonal sense. (b) Attempts to stimulate the reticulo-endothelial activity directly by various biologic stimuli-stimulation therapy. (c) Attempts to achieve this activation of the RES by chemical substances and compounds i.e., to create a pharmacology of the RES.

Substitution Therapy: Stern cited two commercially manufactured products, IG 365 suggested by Fichera (1932-1935) and Splendotherlan, advocated by Braunstein (1933). Neither of these preparations could even partially fulfill expectations. IG 365 consists of autolysates and extracts respectively of spleen and other reticulo-endothelial organs. Its application should restore a balance in the organism, which according to Fichera, is disturbed in cancer patients. Evaluating the results in a great many inoperable tumor cases, he found 7-8% were apparently cured by this method. Subsequent investigations by other authors, Capaldi (1934), Baenz (1934), and Schulte & Luetken (1935), yielded less favorable or completely negative results. Stern believed this could be due to the fact that less effective preparations had been used.

Splendotherlan is a mixture of extracts of spleen and other reticulo-endothelial tissues derived from normal animals, as well as from those which had previously been treated with tumor material. This product is supplemented by the addition of unspecified electrolytes. Clinical use of Splendotherlan had a favorable effect on the general condition of cancer patients. Its use in mice with tar cancer caused an increased length of life, but no influence on tumor development or metastases (Waterman, 1936). Dobrovolskaia-Zarodskaia (1936) and Sephiroff tried Splendotherlan in a strain of mice with hereditary spontaneous tumors. While the rate of incidence of spontaneous carcinomas was 70%, in the controls it was only 40% in the treated series. No effect was observed on the tumors formed in spite of the treatment.

Stern also cited the experiments of Chaletskaja (1936) using previous or simultaneous subcutaneous injection, or intramuscular injection of minced spleen tissue. These inhibited the growth of Erhlich carcinoma transplanted into mice far from the site of the spleen injection. Splenic tissue derived from animals treated with tar for two to four weeks previously did not produce this effect.

Ulesco-Stroganowa (1936) reported that spleen extracts stopped the growth of mouse carcinoma, frequently producing suppuration and subsequent complete involution of the tumor. Histologically severe damage of the tumor tissue and, at the same time, stimulation of the RES was noted. Stern stated that the occurrence of suppuration in these experiments must arouse suspicion that the infected material may have been the real cause of the tumor inhibition.

Hirschfeld and Stark (1937) announced the isolation of an "anti-cancer hormone" from reticulo-endothelial organs, which they called "blasthormone." They stated they had obtained very favorable results in inoperable cancer patients. The tumors became operable in some instances, and sections showed a beginning involution of the neoplastic tissue. No details were given as to the preparation of this "hormone" so confirmation of their reports could not be obtained.

Stern then described the investigations of Lewisohn and Klein (1938-39) with highly concentrated extracts of spleen on sarcoma 180 in mice. Lewisohn noted that

injections of small doses of spleen extract (0.1 cc.) had a somewhat stimulatory effect on the tumor growth. This fact induced the author to stress the importance of a sufficiently large dosage, and to refer to the ineffectiveness of the weak concentrations of spleen extract hitherto generally used. In the animals in which large doses were used, there was considerable enlargement of the spleen (four to five times normal), an effect not produced by any other extract. Lewisohn concluded that the effective extracts do not act directly on the tumor, but indirectly by increasing the activity of the spleen.

As the reticulo-endothelial system can be considered as the active part of the whole mesenchyme, Stern cited the interesting results of Morton and Beers (1935) who prepared extracts from fresh human connective tissue (rectus sheaths) and found this product produced an inhibitory effect on rat tumor 256: complete inhibition of tumor in 60 per cent and marked retardation on 15%. Muscle extracts did not show any influence.

Stimulation of Reticulo-Endothelial Activity: Attempts to increase the reticulo-endothelial activity by adequate biologic stimuli are based on a lesson taught by nature itself. From the phenomenon of inflammation and immunology we know that as a consequence of some pathologic conditions the body increased its resistance not only by activating the preformed reticulo-endothelial elements, but also by transforming various parts of the "resting" mesenchyme into "active reticulo-endothelial tissue. Thus, meeting special requirements of the organism as well as responding to exogenous interferences, the functional activity of the reticulo-endothelial system varies widely, both qualitatively and quantitatively. Correspondingly, the studies concerned with a stimulation of the reticulo-endothelial system in neoplasia tried to achieve this by imitating the natural processes. Some of these experiments made use of the fact that infections stimulate the reticulo-endothelial activity in the initial phase - defense reaction - and also in the stage of recovery - repairing phase. We refer to experiments of Braunstein (1939) with artificial malaria infection of cancer patients, which method, however, did not yield any really favorable results. Roskin (1938) and collaborators reported cures in 70% of mouse carcinomas

after infecting the animals with *Schizotrypanum cruzi* or by injecting them with the toxins of these parasites. This effect was specific, insofar as it could not be produced by infections with *Trypanosoma equiperdum*, *Spirochaeta duttoni* or bacterial endotoxins (Pyrifer). *Schizotrypanum* endotoxin treatment before tumor transplantation prevented tumor development in a high percentage of instances. This fact and histologic findings made it probable that the action of this treatment depends upon stimulation of the reticulo-endothelial system. Probably a similar explanation has to be applied to a great many reported, more or less successful, attempts to increase the resistance of the body to neoplasia by means of nonspecific stimuli (bacterial toxins, Coley's fluid, autotransfusion, etc.). Caspari (1924) advanced in a general way the opinion that most of the agents used for cancer-curative purposes act by liberating "necrohormones" from the destroyed tissue which activate the reticulo-endothelial system and this phenomenon actually was responsible for the inhibition of the neoplasms.

As before mentioned, Markuse, et al. (1936) reported that ultraviolet irradiation of the spleen is also a means of activating the reticulo-endothelial system. Roskin (1934) using this method in animal experiments, observed complete disappearance of the tumor in a high percentage of treated animals. In these experiments, transparent windows were inserted into the abdominal wall of the animals, thus allowing the irradiation of their spleen. As this operation itself is a severe interference with physiologic mechanisms, the objection that no control animals were operated upon in the same way without ultraviolet irradiation is justified (Woglom 1936). A different method was used by Nagumo (1938). This author partially resected the Bashford mouse carcinoma and later ligated the hilus of the spleen. In about 40% of the animals so handled a complete resorption of the rest of the tumor was observed. According to the author, this effect must be attributed to a stimulation of the reticulo-endothelial system by the "necrohormones" of the ligated spleen.

An interesting new way of artificially imitating biologic phenomena was reported by Kolischer (1936). He published experiments, performed in collaboration with Saphir and Horn, attempting to treat tumors with living macrophages. These cells

were segregated from the spleen of animals by means of the Rosenow tissue press and suspended in Tyrode solution where they remained alive for six to eight hours. Injections of these emulsions into rat cancers gave favorable results; likewise treatment of some cancer patients with this method appeared to be promising. According to the author, it would be necessary for this latter purpose to have available large amounts of macrophages, preferably by means of tissue cultures of human macrophages.

On the basis of the aforementioned results of Wetzler-Ligeti and Weisner (1938), another way of a biologic activation of the reticulo-endothelial system seems practicable through the control of the reticulo-endothelial function exerted by pituitary factors. Correspondingly, the "positive restropic factor," isolated by the authors from anterior pituitary as well as from blood, could be used for stimulation of the reticulo-endothelial system. Therapeutic experiments of this kind have not yet been published.

CHEMICOPHARMACOLOGIC ACTIVATION OF THE RETICULO ENDOTHELIAL SYSTEM: Although the biologic chemistry of the reticulo-endothelial system is still less known than its physiology and pathology, some facts are established in this sphere which throw a certain light upon the possibilities of influencing this system by means of defined chemical substances.

From the preceding sections dealing with other therapeutic experiments, as well as from the relations between reticulo-endothelial system and tumor development, the importance of dosage and rate of stimuli whenever the reticulo-endothelial system is concerned is apparent. Therefore, it should not surprise us that the same chemical substances - colloids - which, when administered in large doses cause a "blockade," i.e., a definite damage of the reticulo-endothelial system - are found also to increase its activity, when administered in appropriate smaller doses. This phenomenon

might be explained by a compensatory hypertrophy of resting connective tissue, following the damage of a part of the reticulo-endothelial system. Likewise, it was observed that splenectomy causes a decreased function of the reticulo-endothelial system lasting only a few weeks and being later replaced by a hyperactivity.

These reactions, however, are not very long lasting and dependable. Hence, the few investigations which made use of them for therapeutic purposes have not proved very successful. Kageyama (1937) administered small doses of collargol (colloidal silver solution) to rabbits with sarcoma.

In recent years, independent investigations of several authors detected an activating influence of some biologically important substances on the reticulo-endothelial system. Thus, a stimulation of the reticulo-endothelial function has been attributed to lecithin (1936), a substance found by several authors also to possess a tumor-inhibiting property. This latter fact is not firmly established, however, as in other investigations no antiblastic influence of lecithin was observed.

Moncorps (1933) reported that cytosin increased the colloid-storing activity of the reticulo-endothelial system, even if this system had been previously damaged by injection of India ink. This report was confirmed by Ludany and Sarkany, (1937) who found that cytosin increased the absorption of bilirubin after this function had been impaired by splenectomy. In 1935, in collaboration with R. Willheim, Stern demonstrated that application of colloidal carotene solutions to rabbits stimulated their reticulo-endothelial system considerably and regularly. Independently Ahmed (1935) obtained similar results with vitamin A. A close relationship of this vitamin to the reticulo-endothelial system was also established by studies of Lasch (1936) and Koenig and Wendt (1937). These authors found that the storage of vitamin A in the liver was not impaired by a damage afflicted to the parenchymatous liver cells, but only after experimentally or pathologically produced disturbances of the reticulo-endothelial elements of the liver.

Three years ago, these results induced us to make systematic studies of the activation of the reticulo-endothelial system by defined chemical substances and

eventually to apply these compounds for purposes of tumor therapy. These experimental studies were prematurely discontinued, but as some definite results had been already obtained, a preliminary report is given here.

CONCLUSIONS:

(1) Lecithin is known to be a tumor-inhibiting lipid - in contrast to the neoplasia-favoring quality of cholesterol. All these lipoids are closely connected with the reticulo-endothelial function. Stern planned to extend these studies to other phospholipoids (cephalin).

(2) Vitamin A and its provitamin carotin are of great importance to the intact function of the epithelium; deficiency of these substances in the diet caused epithelial metaplasia. Further, it has been mentioned above that both substances are stored by cells of the reticulo-endothelial system.

(3) The pyrimidine substances (cytosine, uracil) are important constituents of the nucleic acids, the main chemical compounds of the cell nuclei, and therefore, intimately involved in the processes of cell division and growth. In this respect, Stern believed it would certainly be necessary (a) to include in these studies other natural and synthesized pyrimidine derivatives, studying their effect on the reticulo-endothelial system and (b) to extend these investigations generally on the relationship between the reticulo-endothelial system and normal growth, a sphere of physiology which hitherto had not yet been attacked, but which might yield interesting results. And, as it has again been justifiedly stressed, the investigation of characteristics of the cancer cell belongs in the field of cell physiology, and the understanding of the process must be dependent upon the advance in the understanding of growth and differentiation of normal cells.

Concluding this discussion of attempts to increase the reticulo-endothelial function in the interests of cancer therapy, it can be stated that some of the reported studies have yielded promising results in animal experiments. Even when these results will have been definitely established and confirmed, however, the possibility of their clinical use will have to be judged as cautiously as many other

procedures successfully used in animal tumors, which failed to prove their value in human cancer. In general, it can scarcely be expected that even a successful "reticulo-endothelial therapy" of neoplasia will be able to give us more than a measure of support to the established surgical and radiotherapeutic cancer treatments by increasing the resistance of the organism against neoplasia. It need not be stressed, however, that such an achievement would present a desirable advance in our aims, especially if by these means we can control cancer growth for a longer time, thus preventing recurrence and metastases. (Stern, 1941 - he gives 70 references)

Stern (1960) reported a generally decreased RES activity in strains of mice characterized by a high incidence of cancer or leukemia than in strains in which tumors occur rarely.

Stern and Duwelius (1960) concluded that "a) RE phagocytosis may be increased or decreased in tumor-bearing animals, with the direction and extent of the change dependent on, one, several or all of the following variables: 1) animal species, type and site of tumor, stage of tumor growth, type of colloid, method of assay; 2) phagocytic activity may be increased in RE cells of one organ, and decreased or unchanged in those of another; 3) tumor-bearing animals in which increased RE phagocytosis is observed may at the same time exhibit decreased antibody formation, a biologic function presumable involving RE tissues. . . at present one may refer merely to disturbances of certain RE functions in neoplasia, the causal relationship to cancer is still in need of a great deal of continued experimental investigation."

Halpern and his colleagues in Paris were among the first to stress the importance of the reticulo-endothelial system in resistance to cancer. (Biozzi et. al., 1958; Halpern, 1963)

In the past dozen years a number of able investigators such as Black (1958-1965), the Fishers, and Old and his colleagues have become interested in the RES as it relates to host resistance to cancer.

Fisher and Fisher (1961) studied various factors which influence hepatic metastases, one of which was an evaluation of the effect of reticuloendothelial interference. They found that a saturating dose of either India ink or thorotrast, prior to or within 24 hours after intraportal injection of Walker 256 carcinoma cells, resulted in an increased incidence and size of artificially induced hepatic metastases. They noted in 1962: "The fate of the circulating tumor cell may be determined by a number of host factors, and the phenomenon of metastasis formation is not an autonomous one. . . . It is no longer tenable for the cancer surgeon to concern himself only with the surgical gymnastics involved in radical tumor excision. He must be equally concerned with the biologic nature of cancer so that sur-

gical therapy may continuously adjust to our increasing knowledge."

The advances in our knowledge of the viral etiology of neoplasms by such investigators as Bittner, Duran Reynals, and Gross, and more recently by others including Old, Morton and all those working on Burkitt's lymphoma are of very great interest in connection with the study of the reticulo-endothelial system and resistance to bacterial and viral infections and to neoplastic diseases.

Numerous observations indicate the intimate connection of the reticulo-endothelial cells with the defense reactions of the body against infections, both bacterial and viral. The origin of most of the immune bodies has been traced to these cells. The following functions have been attributed to the RE cells in connection with infections: first, the phagocytosis and intracellular destruction of the micro-organisms; second, the reception, detoxification and digestion of waste products that are formed during the process of inflammation, including the toxic products liberated from the bacteria; third, the absorption of soluble toxins; and fourth, the secretion of antibodies.

Old et al. (1960) noted that transplanted tumors induce characteristic changes in RES activity in mice. Zymosan, BCG and other bacterial products induce RE hyperplasia, enhance the capacity to produce antibody and decrease susceptibility to bacterial challenge and to challenge with Sarcoma 180. Survival time is increased twofold in BCG-infected hosts inoculated with Ehrlich ascites carcinoma. Significant retardation in growth of carcinoma 755 and prolonged survival time are seen following BCG infections of either hybrid or isologous C57BL mice. (Old, 1960)

Other recent experiences have suggested that the lympho reticulo-endothelial system is more active in strains of mice with a low incidence of spontaneous tumors than in "high cancer" strains. (Stern, 1960)

Mizuno et al. (1968) reported that intracutaneous injections of the lipopolysaccharide of *Proteus vulgaris* was found to markedly stimulate the reticulo-endothelial system of mice and rats and have a marked antitumor effect in mice bearing the solid type Ehrlich carcinoma and sarcoma 180. Of the various routes of injection tested the most effective appeared to be the intracutaneous. Hager (1969, personal communications) has also found that *Proteus vulgaris* endotoxins are effective in the Ehrlich ascites carcinoma.

Graham and Graham (1955) stated that in the past, cancer has been regarded as an autonomous process, against which the individual is incapable of protecting himself. A number of observations have cast doubt on this assumption. They presented evidence that the body is capable of some defensive behavior toward the tumor, as shown by the elaboration of specific antibodies.

Host resistance to a tumor is implied by a number of observations. The late recurrence of cancer of the breast after 10, 20, or 30 years that so frequently occurs in association with or following a concurrent illness, such as acute cholecystitis or respiratory infection, has been noted repeatedly. The frequent finding of healthy cancer cells on the gloves after an apparently clean axillary dissection in cancer of the breast and the continuing presence of malignant cells in the vaginal smear for several weeks following radical hysterectomy for cancer of the cervix in cases subsequently "cured" suggests that cure is not necessarily dependent upon 100% removal of the cancer tissue. The occasional rapid growth and dissemination of a cancer injudiciously exposed to too much ionizing radiation is a function of the impaired normal tissues. The self-healing epitheliomas are rare, but are nonetheless important demonstration of the effectiveness of host resistance. The wide fluctuation in growth of malignant tumors under varying circumstances in the same individual is much more likely to arise from alterations in the patient's resistance than from fluctuations in the virulence of the tumor. "Spontaneous" regression of malignant neoplasms is authentically and repeatedly recorded. The majority of these occur in conjunction with acute infections, while others have not recognized asso-

ciated outside influence. Active immunity to a transplantable tumor may be elicited in animals by the slow destruction of a growing implant in the host. Repeated injections of dilute formalin or temporary ischemia that produces atrophy of the first implant is followed by resistance to subsequent implants. Attempts to produce a similar immunity in man by autovaccination have not been particularly successful.

The histological appearance of many tumors suggests host opposition. Carcinoma of the uterine cervix is almost always found with its underlying, predominantly lymphocytic, inflammatory infiltration. Steiner et al. have emphasized the characteristic appearance of lesions in gastric-carcinoma patients who survive five or more years. These tumors have a well circumscribed en bloc margin that elicits a chronic inflammatory response. Significantly, these same tumors show degenerative changes in the peripheral tumor cells where one might expect to find the effect of a hostile environment rather than in the central part of the tumor that would be most vulnerable if impaired nutrition were the reason for degeneration. The serum proteins of many individuals with well-established cancer behave as though a chronic infection were present, with an elevation of the globulins and fibrinogen. These evidences of defence disappear as the tumor advances and the patient's health deteriorates. It is probable that a number of "cancer tests" based on physical behavior of the plasma proteins and also on red-cell-agglutination patterns are ultimately dependent upon an immunological response.

Host resistance to neoplasm is predicated upon a difference between the tumor and the host, a difference in the cancer that is capable of irritating or disturbing the host. Mechanical presence of a foreign body or of foreign cells is incapable of eliciting an effective defensive reaction unless it is accompanied by a chemical stimulus. This is demonstrated by the quiescent acceptance of Vitallium or certain types of stainless steel in the tissues because they are chemically inert in that medium, whereas other alloys, equally tough but slightly soluble, are irritating and incite a defensive reaction. A cancer is incapable of eliciting a response simply by occupying space. It must have a chemical composition that is different from the normal tissues. Qualitative differences between malignant and nor-

mal tissues are not demonstrable chemically. However, neither are the group-specific substances of blood types recognizable by chemical means, yet they are easily distinguished immunologically. The demonstration of immunological host-tumor differences in humans has never been very convincing. Scattered reports of success have lacked confirmation. Attempts have been made to demonstrate tumor antibodies, and a common circulating tumor antigen. The bulk of this work upon humans has been centered on a search for a diagnostic method that would detect all patients with cancer. Much immunological work has been done on animals with transplantable tumor. Unfortunately, this is entirely valueless in human cancer. The essential host-tumor relationship can only be studied in spontaneous tumors - and preferably in humans.

It has been noted that such organs as kidneys, liver, spleen and brain have specific components not found in other tissues and that these characteristic substances, when properly reinforced as a vaccine, are capable of eliciting an active or passive immunity that destroys the function of that organ. If these subtle yet potentially effective differences exist between normal tissues in the same individual, it is reasonable to expect that similar differences may be demonstrable between a tumor and a nonmalignant tissue. (Graham & Graham, 1955)

Stoerchand Eisen (1946, 1947) noted that there is suppression of circulating antibodies in pyridoxine deficiency. Pyridoxine deficiency caused almost complete loss of lymphoid cells with an inability to form circulating antibodies in albino rats. This finding suggests the advisability of administering pyridoxine to cancer patients.

In the light of the data reviewed above, suggesting the importance of antibodies and an intact RES, it is not surprising to find that some observers are questioning the results obtained by conventional methods of treating cancer.

Jones (1956) suggested that cases of cancer untreated (by surgery or radiation) are perhaps longer-lived than the treated cases, and "the evidence is strong enough to warrant full attention to this part of the cancer problem, for not only is there

complete uncertainty of the efficacy of cancer treatment today, but there is also the possibility that survival tendency is less with treatment. It is most likely that, in terms of life expectancy, the chance of survival is no better with than without treatment, and there is the possibility that treatment may make the survival time of cancer cases less." He added: "There is hope that identification of carcinogenic factors might lead to an eradication of cancer on a prophylactic basis."

The following review by Cohen (1956), a radiologist in Johannesburg, South Africa, clearly summarizes the factors by which the mammalian host influences the rate of growth and dissemination of tumors.

He stated that clinical cancer management is still limited to surgery and radiotherapy. "While both these methods are more or less efficacious in eradicating the primary lesion. . . most patients so treated still die of disseminated malignant disease. It seems unlikely that the principles of surgical and radiotherapeutic practice could be extended so as to cure those cases for which current technics are not adequate. Indeed, far from improving our results, attempts to extend the treated zone frequently diminish the probability of cure."

The next important step in the control of cancer is to investigate those factors by which the mammalian host influences the rate of growth and dissemination of tumors.

The resistance of the host against his tumor can be modified by many physical, chemical and physiological factors. Murphy first proved that the reticulo-endothelial system, in particular the lymphocyte, exerts a controlling influence on tumor growth. Agents stimulating the production of antibodies were able to enhance the host's tumor-resistance, often to the point of absolute immunity.

The converse effect - abrogation of natural or acquired resistance to tumors - is easily produced by factors inhibiting the reticulo-endothelial function, such as total body irradiation, blockade of the reticulo-endothelial system with colloids, administration of cortisone and allied drugs, overwhelming doses of antigen in the form of liophilized tumor, neurogenic stress, or local trauma, irradiation or intoxication. All of these agents can promote the onset of tumors, facilitate

their growth and dissemination and inhibit their response to treatment suggesting that immunologic processes might affect the pathogenesis of cancer in man and its prognosis.

IMMUNOLOGIC MECHANISMS IN THE PATHOGENESIS OF CANCER: Cancer cells contain genes, antigens and enzymes other than those found in normal tissue and are consequently subjected to immunological homeostatic control. For this reason single cancer cells or isolated small groups cannot in themselves give rise to malignant tumors; a certain critically large number of cells is required before tumor growth can commence.

It would seem that most adults must possess many small groups of isolated neoplastic cells persisting for long periods as "sub-critical colonies."

There is evidence too that the host may continue to exert some restraining influence on the growth of established tumors. A frequent finding at autopsy in cancer cases is the presence of many tumor-cell emboli which have evoked an acute inflammatory reaction and are in the process of dissolution. Similarly, one not infrequently observes a patient who develops distant metastases 15 to 40 years after operation for the primary growth.

"Both, therefore, in the healthy adult carrying sub-critical or precancerous foci and in the locally cured patient with sub-critical or dormant metastases, those factors which might effect local or systemic resistance are of the first importance in determining future survival. Since these factors are readily influenced by trauma, stress, radio-diagnostic procedures and medication, they fall within the scope of everyday medical practice."

Cohen then discussed various carcinogenic agents and local and systemic promoting factors or co-carcinogens.

Almost any form of trauma, chronic irritation (croton oil, surgical incision, injection of foreign material) have been used experimentally as co-carcinogens.

Excision of a primary lesion is often followed by several new primary tumors, sometimes thought to be recurrences, arising in the surgical scar in sites known to harbor other precancerous foci, i.e., multiple papillomatosis of bladder.

Systemic promoting factors include colloidal materials which blockade the reticulo-endothelial system, such as India ink, trypan blue, ferric saccharate, and thorium dioxide sol; agents that produce lymphopenia such as total body irradiation, virus infections like influenza; mitotic poisons and similar drugs used for cancer palliation, including mustard gas derivatives, folic acid, purine and amino-acid antagonists (aminopterin, azoquanine and sarcolysin); synthetic vitamin K analogues (menadione or synkavit); hormones like pituitary corticotropin and possibly certain adrenal steroids, and all severe injuries, debilitating illnesses, pregnancy and major surgical procedures, collectively classified as "stresses" although many of these agents have been observed to inhibit temporarily the growth of established tumors - hence their reputation as palliative agents, they tend, in general, eventually to accelerate tumor proliferation and dissemination.

From the practical point of view, it is the obvious duty of every physician to prevent as far as possible, the onset of cancer by minimizing exposure to suspected or potential carcinogenic agents, eliminating all non-essential diagnostic radiographic examinations in younger members of the community, avoiding all forms of radiotherapy or administration of radioactive isotopes for non-malignant conditions, unless a serious threat to life makes such exposure essential, insuring adequate protection of the community from radioactive products, discouraging smoking and similar suspect habits, and urging control of smoke, soot and motor exhaust fumes. The older members of the community who presumably already carry precancerous foci, and in particular apparently cured cancer cases who may carry dormant tumor-cell nests, should especially not be exposed to promoting factors such as corticotrophic, gonadotrophic and sex hormones, any of the known cancer-palliative drugs, avoidable trauma, and stress-inducing operations. Chronic irritations should be corrected.

HOST RESISTANCE AND RESPONSE TO THERAPY: The significance of systemic immunity in clinical cancer control is nowhere better illustrated than in the response of tumors to irradiation.

Doses from 10 to 100 times greater are necessary to destroy cancer cells in vitro.

Any factor tending to isolate a tumor from its vascular and cellular elements in its bed will prevent its regression following otherwise adequate radiation. Tumors in avascular scars and ulcers, particularly in the devitalized scars and necrotic ulcers from previous radiation are notoriously radioresistant. Similarly, factors inhibiting systemic immunity such as total body irradiation or mitotic poisons, including cortisone and nitrogen mustard and azoquanine, will all render tumors incurable by radiotherapy. Even the so-called radiosensitizing agents, such as menadione or "synkavit" will, in fact, prevent complete regression of adequately irradiated tumors.

Further, when extensive or deep-seated tumors are irradiated, the correspondingly large volume-dose itself induces a leukopenia and inhibits the reticulo-endothelial function, with the result that such tumors often fail to respond to ordinarily curative doses. The systemic resistance factor thus sets the upper limit for size and depth of tumors curable by radiation.

The converse of this effect, that is the enhanced radiosensitivity when host resistance is stimulated, has only recently been demonstrated with homozygous tumors grown in genetically modified heterozygous hosts, with a mutant tumor grown in homozygous hosts and with tumors grown in hosts specifically immunized against them. These effects point to the future possibility of specifically immunizing the human host against his own tumor, thus enhancing its curability by radiation and possibly also preventing or delaying the development of metastases.

Cohen then gave two very interesting case histories. In the first there was widespread metastases of a high-grade rapidly proliferating carcinoma. In this case 24 nodules were treated by small fields of superficial radiation (small, single doses of 300 to 2000 r): 17 disappeared. The patient remained quite well in the five year period in which she was followed and was symptom-free eight years after onset.

The second case was a squamous cell carcinoma of the dorsum of the left hand, of two years' duration. The patient was a male mechanic (European), of Johannesburg,

Union of South Africa. The tumor had been present two years and had been treated by superficial radiotherapy. Seven months later there was obvious local recurrence and involvement of the epitrochlear and axillary lymph nodes. All three sites showed squamous cell carcinoma on biopsy and were treated by intensive radiation. For the next six months he was well except for a small necrotic ulcer at the primary site.

He then suddenly developed a febrile constitutional reaction with a generalized macular rash. The skin rash faded within a few days, except for those lesions inside the irradiated areas which persisted and increased.

Some weeks later each macule within the irradiated skin-fields had developed into a palpable tumor. The lesions became confluent, forming two rectangular tumor masses exactly demarcating both axillary treatment fields. Biopsy of these lesions showed unpigmented malignant melanoma! Although the primary melanoma was not found, as the patient died shortly thereafter without necropsy, there can be no doubt that widespread melanoma-cell embolization had occurred, but that all tumor emboli were effectively suppressed except in those tissues where local resistance had been impaired by the radiation. (Cohen, 1956)

Malmgren et al. (1952) reported on the effect of carcinogens and cancer chemotherapeutic agents upon antibody formation in mice. They noted that the antibody depressing effect of certain carcinogens, nitrogen mustard, x-ray, Rous sarcoma virus, and the chemotherapeutic agents cortisone and benzene is well established. They then tested the carcinogens, urethane, methylcholanthrene, 1, 2, 5, 6-dibenzanthracene, 1, 2-benzanthracene, and 4-dimethylaminoazobenzene, given subcutaneously three times in a 12-day period. A 4% suspension of sheep red cells, used as antigen was injected intraperitoneally 5 days before the sera were harvested. These carcinogens all depressed the hemolysin titres, while the non-carcinogenic analogs of these compounds (methylcarbamate, phenanthrene, and 4-diethylaminoazobenzene) did not affect the formation of antibodies.

The chemotherapeutic agents, allopurinol, A-methopterin, 2-6-diaminopurine, podophyllotoxin, sodium arsenite, and triethylmelamine all depressed antibody formation. One compound, furacin, did not lower the antibody titre.

Since passive antibodies in vivo and in vitro were not affected by any of these compounds, it is inferred that they act by interfering with normal antibody production.

The possibility that the lowered hemolysin titre was due to general systemic activity was ruled out. Maximum tolerated doses of NaCN and CuSO₄ did not decrease antibody production. Further, the administration of a carcinogen and its noncarcinogenic analog in amounts of equal toxicity resulted in inhibition by the carcinogen only.

Antibody inhibition at the site of antibody production appears to be a property common to these carcinogenic and cancer chemotherapeutic substances.

Among the first to become aware of the problem were Moore and Kondo (1958) who reported that there is experimental evidence that these toxic compounds may indirectly accelerate tumor growth by inhibiting normal defense mechanisms.

Molomut, et al. (1952) were perhaps the first to report the induction of metastases from a heterologous tumor in mice as a result of cortisone.

Bradner & Clarke (1959) reported that low doses of zymosan stimulates resistance to sarcoma 180 but that a single dose of 150 mg/kg of hydrocortisone acetate injected at various times after tumor implantation could completely block at nine days, partially block at 13 days and not affect at two days the tumor regression which normally occurs after zymosan treatment. Zymosan given at various times from two weeks before implantation to two weeks after revealed a diversity of response but the greatest number of regressions occurred in animals treated one to seven days after implantation. Their results suggested the existence of an early (non-specific?) phase and a later acquired immunity phase in the host defense process.

More recent reports include those of Stjernsward (1965) and Martin et al. (1960-64). Others such as Preston et al. (1961) conditioned animals for tumor transplants with cyclophosphamide, cortisone, and other cancer chemotherapeutic drugs. The results show a markedly increased mortality in the conditioned animals.

Of special interest in this connection are the increasing numbers of inadvertent transfer of various forms of cancer with cadaver renal transplants in the recipients who were under immunosuppressive therapy in order to prevent rejection of the grafts. (D.C. Martin et al. 1965) One especially interesting report by Wilson et al. (1968) described a case in which the inadvertent transfer of an epidermoid carcinoma of the bronchus with a cadaver renal allograft provided a unique opportunity to observe its sudden appearance and rapid growth and its equally rapid regression after immunosuppression was terminated.

A number of physicians have become concerned over the many reports in which corticosteroid therapy is blamed for acceleration or spread of a malignant tumor. Kelly (1959-1963) has reviewed the subject very thoroughly. He noted that soon after the introduction of cortisone the American Medical Association appointed a subcommittee to study the effect of the drug on patients with cancer. It concluded that, although some felt better for awhile, "in several cases, despite the subjective response and improved appearance of the patient, there was evidence of the more

rapid spread of the neoplasm."

Southam (1968) stated: "It is formally established that many cancer patients have impaired immune responses. Iatrogenic immunosuppression contributes to this impairment in many patients but the data indicate that there is also an impairment which is related to the neoplastic disease per se. The defect appears to be in responses requiring the mediation of cells, rather than in those which are dependent upon the production and reaction of serum antibodies. The immunologic deficiency is most frequent in patients with widespread and debilitating cancer, but it is not a consequence of the debility alone."

Reiner & Southam (1967) reported on the increased growth of tumor isotransplants after immunosuppression of the recipient once by methotrexate or 5-fluoro-2-deoxyuridine.

Page et al. (1962) reported on the anti-inflammatory effect of 6-mercaptopurine which appears after one to six weeks' treatment, depending on the dosage. This effect could not be correlated with leukopenia or weight loss. Borel and Schwartz (1964) observed a distinct anti-inflammatory action of 6-mercaptopurine and reported that it affects delayed hypersensitivity to a greater degree than it inhibits humoral antibody formation.

Among the immunosuppressive drugs in addition to the corticosteroids are the alkylating agents, the halogenated pyrimidines (5-FU and BUDR), the folic acid antagonists (methotrexate), 6-mercaptopurine, actinomycin D, cytoxan and A-methopterin. With each of these agents immunologic suppression persists for weeks up to 24 months after discontinuance of the drug, depending upon the species and the test antigen. Continuous drug treatment is not needed to maintain the state of immunologic tolerance.

These factors must be taken into consideration in planning clinical trial of immuno-stimulating agents such as bacterial toxins, BCG, zymosan, etc. for if the immunosuppressive drugs or radiation are given first, the patient does not usually respond to toxin therapy nearly as well.

In an editorial Strauss (1961) asked: "Does extensive surgery for malignancies have to be re-evaluated?" He reported that analysis of clinical observations over a period of 51 years in over 6000 patients operated upon for carcinoma of the breast, stomach, colon and rectum indicated that each individual has his own resistance against his own cancer and that this is more important in the survival rate than any other single factor. It would also appear that this resistance factor has greater significance than any classification or grading of malignancies. He added that electrocoagulation, both in clinical cases and in laboratory animals, has confirmed this concept. In Belgian hares and white rats, it was shown that electrocoagulation of a malignant tumor resulted in necrosis of cancer cells the products of which were absorbed slowly and acted as an antigen, thereby producing a demonstrable immunologic effect which increased host resistance and the animals then were able to reject subsequent tumor challenges. Similarly, antigens resulting from necrosis of cancer cells produced by crushing clamps and ligation of bleeders during surgery or following cobalt, x-ray, radium and toxin therapy may enhance the inherent natural immunity of patients. Strauss' many publications deserve serious study. (Strauss 1933-1969)

These antigens may have been responsible for the spontaneous regressions observed following exploratory laparotomy or incomplete excision of inoperable tumors. Braun & Kessel (1964, 1967) have studied the beneficial effects of DNA breakdown products and also the effects of bacterial endotoxins in stimulating host resistance. They report that materials released from certain mammalian cells by various means can enhance the rate of increase in antibody-forming cells and usually also the rate of clearance of particulate antigens. DNA digests can restore responses of animals in which antibody formation has been impaired by irradiation or by immunosuppressive drugs. They added: "Bacterial toxins can produce a similar stimulation in the absence of antigen evoking a rapid increase in pre-existing hemolysin - or bactericidin - forming cells, for example. Since we have evidence that endotoxins may act in this fashion by releasing oligodeoxyribonucleotides from intracellular sites, this

difference in antigen requirements between endotoxin and the other stimulatory agents was puzzling. We, therefore, considered the possibility that two factors are required to stimulate antibody-forming cell populations: (1) the actual stimulator and (2) an agent permitting the entrance of the stimulator into the cells to be stimulated. Endotoxin, with its known effects on cell integrity and on permeability may possess both attributes."

These considerations may explain why streptococcal infections were responsible for the majority of dramatic "spontaneous" regressions for they produce hyaluronidase, streptodornase and streptokinase. These ^{streptococcal} enzymes undoubtedly affect the permeability of the tissues and cells ^{more} than ~~the~~ other types of infections. Unfortunately, ^{some of the preparations of} the methods used to make the mixed bacterial toxins (Coley) undoubtedly destroyed these enzymes. Possibly in the future preparations of various endotoxins may include these enzymes or dimethyl sulphoxide in order to potentiate their rapid penetration.

A number of other surgeons have recently questioned the wisdom of performing prophylactic lymph node dissections. For example in the treatment of malignant melanoma Catlin (1954) stated: "We found no evidence in our material to support the theory that radical operation made in all cases will produce better results. Block and Hartwell (1951) stated: "We found no evidence in our experience that, in the absence of clinically positive nodes, a prophylactic node dissection is better or worse than local excision alone. . .and we disagree with the dogma of Pack that elective or prophylactic lymphadenectomy must be done routinely to adequately treat malignant melanoma." These authors cited several other authors including Lund and Thren who believe that therapeutic lymph node dissection is of no use. Olsen (1964) reported that in 112 patients with malignant melanomas of the extremities, excluding the hands and feet, and in the abdominal wall, but without clinical signs of metastases, metastases to the regional lymph nodes developed more frequently in those patients in whom the underlying fascia had been removed, as compared with patients in whom it had been left intact: 45% and 8-14% respectively.

As regards the treatment of breast cancer, as early as 1954, Garland reported that radical mastectomy may actually shorten the survival time of some patients, and

he recommended simple mastectomy and radiotherapy as being adequate and with a lower morbidity rate.

Since about 1905 few surgeons have considered the importance of stimulating or conserving the lymphatics but McCullough (1908) believed they were an important link in the host's defense mechanisms against cancer. He advised not excising them but stimulating them to produce antibodies.

Crile (1957) believed there is a place for a graded approach to surgical treatment of cancers of the lip, malignant melanoma or thyroid cancer: "There is no statistical proof that prophylactic resection of regional nodes is more likely to control the cancer than is therapeutic resection soon after regional metastases are palpable. . . .Cancers low in the rectum. . . .can be successfully treated by electrocoagulation. If they are not thus controlled, a combined abdomino-perineal resection still can be done. Similar graded treatment can be applied to small cancers of the tongue and gingival margins, to cancers in situ of the cervix and to Stage I cancer of the breast without palpable nodes - all well adapted to local eradication, to accurate follow-up and hence to graded treatment. When a limited operation has a good chance of controlling a disease and when this limited operation does not jeopardize the success of a subsequent more extensive one, it may be best to try the simpler operation first.

More recently Crile (1965, 1967) has advocated conservative surgery for breast cancer. He stated: "It is time that we take steps to eliminate the needless morbidity associated with the treatment of breast cancer. Standard radical mastectomy is not indicated unless axillary nodes can be shown to be involved and even then a modified operation in which the nodes are dissected without removal of the muscles probably will give as good a result with less morbidity. Regional nodes are important to immunologic resistance, and this 'immunity' may be destroyed by either removal or irradiation. . . .To remove these nodes or to irradiate them might remove an essential part of the patient's immunologic resistance." Crile's recurrence rate is lower after simple mastectomy than after the radical procedure.

In addition to avoiding radical mastectomy Grile cut thick skin flaps; leaving as much as possible of the subcutaneous fat to preserve the blood and lymph vessels. He stated that the removal of axillary nodes in the classic radical mastectomy may cause stasis of lymph in the skin and thereby trap cancer cells.

"Since it is likely that in most cancers of the breast malignant cells are widespread in the blood and lymph draining the part, it maybe more important to preserve the integrity and resistance of the tissues than to try to mechanically to remove tumor cells. He added that another possible explanation of the low incidence of local recurrence is related to the fact that the axillary nodes were not disturbed and the incidence of local recurrences at five years fell to 5% of 153 cases. He concluded: "Although the numbers are too small to be of statistical significance, the diminished incidence of recurrence when the nodes were not removed suggests that removing them stimulates local recurrence.

"The frequency of recurrences of breast cancer in the skin of arms afflicted with post-operative lymphedema, suggests that in breast cancer, too, stasis of lymph after dissection of regional nodes could be a factor contributing to the increased incidence of local recurrence."

McWhirter in Edinburgh (1957) has reported his excellent results in treating breast cancer by simple mastectomy and post-operative irradiation.

Very few surgeons have considered the possibility that by operating very early in the course of cancer we may not allow the growth time to evoke the host's immune mechanisms. Possibly one reason the end results were apparently better in the period from 1850 to 1900 as compared to 1910 (Korteweg, 1910, p. 16 and pp. 23-24) was that the older surgeons such as Billroth, Esmarch, Volkmann, Von Bergmann, etc. operated much later in the disease and did not perform such radical surgery. Korteweg contested the usefulness of extensive operations believing that the modern fashion of radical surgery is doing more harm than good, because these very extensive operations paralyze the general resistance of the wound for a longer time, thereby favoring the development of recurrence or metastases. Korteweg did not consider the role of suppuration and post-operative infections which were much more

prevalent prior to 1900 and which helped stimulate resistance against recurrence or spread of the neoplasm.

W.B. Coley (1910, 1917, 1921) was apparently the first to advocate conservative surgery for sarcoma or giant cell tumor of the long bones, and by his method of resection or curettage combined with adjuvant toxin therapy (given to help prevent recurrence or metastases) he succeeded in saving a considerable number of limbs. However, in osteogenic sarcoma he advocated amputation plus toxin therapy. By this method he doubled the five-year survival rate over surgery alone. (W.B. Coley, 1933)

B.L. Coley (1941) reported on this subject: "Conservative surgical measures are applicable to most benign tumors of bone. While the majority of operable malignant tumors primary in bone require radical surgery. There is a small minority in which less radical methods are justified. The latter include excision, segmental resection, partial resection, total scapulectomy and partial amputation of the hand and foot. The useful limbs that are salvaged by the less radical measures justify the occasional failure which such a policy entails.

B.L. Coley & Higinbotham (1948) in reviewing the subject further stated: "conservative surgery for tumors of bone implies the substitution of some less radical procedure than amputation, or if the latter is unavoidable, amputation at the lowest level compatible with safety. Curettage, partial resection, segmental resection and excision are methods which may at times be used in lieu of amputation. If these procedures are successful in eradicating the primary tumor and in avoiding a local or regional recurrence, they may then be considered as wholly justified. Certain histological types and certain clinical and roentgenological settings indicate the advisability or the inadvisability of attempting conservative measures. High thigh amputation for osteogenic and chondrosarcoma of the lower femur may be a safe substitute for hip disarticulation and offers greater advantages to the patients who survive. It would seem to be worthy of our concentrated effort to perfect the operative treatment of bone neoplasms by every available means. One important advance might be the exercise of better care in the selection of cases in which less radical

surgery would accomplish complete removal of the tumor with less mutilation, thus affording the patient a better opportunity to lead a more normal life." (D. L. Coley, 1946)

We believe that if an immunostimulating adjuvant such as BCG or bacterial toxins is used prior to as well as following surgery for malignant bone tumors that far more conservative surgery may prove effective in producing permanent results in these patients.

Zeidman et al. (1950-1965) studied factors affecting metastases. They noted that the number of embolic tumor cells is an important factor. Their mortality, especially in resistant hosts is very high. The number of metastases is not apparently related to the final size of the primary (1950). They then studied the effectiveness of the lymph node as a barrier to the passage of embolic tumor cells and found that a lymph node can function as a trap for tumor cells and may prevent their further spread beyond the affected node for weeks or months (1954). However, although the first cancer cells to arrive in a lymph node may be destroyed, later, repeated or even regular emboli can overcome the destructive capacity of the nodes (1965).

The reason why acute concurrent infections, Coley toxins, yeast extracts, or BCG seem to exert such a favorable effect in preventing recurrences or metastases may be their ability to maintain the lymph nodes in a more reactive condition, especially if such therapy is prolonged for more than a few weeks, so that any tumor cells arriving in the lymph nodes somewhat later will find the nodes still capable of destroying the embolic tumor cells.

Tjernberg and Zajicek (1965) noted that the barrier function of lymph nodes, in trapping and destroying tumor cells, was found to be reduced after local irradiation. In citing these authors Strauli stated: "No single influence, however mechanical or biological, could be held responsible for this effect, which was ascribed to an interaction of several factors. As a whole, the question of the biological facet of the barrier function, in contrast to the purely mechanical part of the problem remains open for discussion. One of the major gaps in our knowledge of

tumor dissemination is therefore unveiled. This uncertainty has important clinical implications concerning, for instance, the role of irradiation and chemotherapy in the lymphatic spread of cancer." The transport of damaged tumor cells in the lymph may not result in metastasis formation but may have considerable immunologic consequences. (Strauli, 1967)

Lehmann (1955) discussed the case for rational surgery in cancer. "Bring on degeneration of cells (normal or malignant) in a tumor and its resorption will start. Continue stimulation after suitable intervals - to allow the reaction to take its course and regression will be complete. There is nothing miraculous or specific about it. A malignant tumor regresses when and as long as products of tissue degeneration are present to keep the resorptive inflammation going, provided the reacting tissues are left undisturbed and are not destroyed by irrational methods of treatment.

"In other words methods of cancer treatment work by stimulation of the natural healing process... .

"That the toxins liberated by bacteria cause tissue degeneration followed by inflammatory reaction no one can deny. Nor can we dismiss the recorded observations of the older surgeons that during certain infections malignant tumors can regress and heal 'spontaneously'. Erysipelas was undoubtedly a frequent event after operations in the old days, and when a patient went through such an attack his tumor sometimes showed remarkable regression. Nowadays, we see no erysipelas in our wards, and if it occurred - it would have no chance to act on the tumor because its natural, prolonged course would immediately be aborted by antibiotics. ^{Escherichia} Coli infection has also been recognised as beneficial in cancer. Grey Turner (1943) found it significant that those cases of carcinoma of the colon which were complicated by abscess formation often did extremely well.

"It seems that the extensive and mostly prophylactic use of antibiotics in cancer surgery must be depreciated; it is not rational and should be reserved for emergencies. When dealing with cancer, infections should not be repressed, but tolerated

if not even invited. It was a shrewd idea of the surgeon, Coley, to try to imitate the action of infections by injecting toxins near the site of a malignant tumor. He and his followers were handicapped in their work by the prejudices of their time, most of the patients in their trials were unsuitable for this kind of therapy owing to mutilating orthodox treatment they had received before." (Lehmann, 1955)

RADIATION AND RESISTANCE TO CANCER

Murphy and his colleagues (1915-1926) at Rockefeller Institute were among the first to make extensive studies of the apparently deleterious effects of irradiation on lymphoid tissues and thus on host resistance to cancer. They noted that the dose of irradiation was the crucial factor, for very small doses could increase resistance, by the inflammatory reaction they induce, while larger doses destroyed it. Since then hundreds of reports have appeared on the carcinogenic, leukemogenic and sarcogenic effects of various forms of irradiation, often administered for diagnostic purposes or for benign conditions such as ankylosing spondylitis, cosmetic problems or thymus enlargement. Space does not permit us to enumerate all these references since the problem is now fully appreciated and radiologists are much more cautious in eliminating poorly protected equipment, in avoiding unnecessary diagnostic fluoroscopies or in treating benign conditions.

Pelner (1957) stated that "A review of both old and recent work on the effects of ionizing radiations on the tumor and the host suggests that our conception of proper dosage may have to be revised. Large doses of radiation may have a salutary effect upon the local tumor but a detrimental effect on the resistance of the host."

Recently Martin et al. (1970) reported on 368 patients who developed cancer in the facial or neck skin who had previously been irradiated for benign conditions. They stressed the hazards of even moderate dosage for benign lesions. Latent intervals as long as 64 years suggests that the risk of cancerogenesis in irradiated skin persists for the life of the patient. There were 35 patients (i.e., about 10%) who died as a result of uncontrolled radiation-induced skin cancer.

It is important that agents which may protect the host against the deleterious effects of radiation, without also protecting the tumor cells, should be used. In recent years a number of substances have been tried which have proved helpful, i.e., adenosine triphosphate, beta-aminoethylisothiouronium (AET), cysteine, epinephrine, foreign proteins including phytohemagglutinin, horse serum, certain lipids such as olive oil, pyrimidine, RNA breakdown products, tissue extracts including bone marrow, spleen or embryonic tissues, pectin; certain vitamins, i.e., pantothenic acid, rutin,

pyridoxine, B6; and yeast extracts. Perhaps the most promising agents appear to be bacterial toxins and yeast extracts. Ainsworth and Chase (1959) were among the first to study the radioprotective effects of thermostable antigens of *Proteus morgani*, *Klebsiella pneumoniae* or *Escherichia coli* or *Pseudomonas pyrogenes*. (Ainsworth and Forbes, 1961). Soluble antigens from gram positive bacteria were ineffective. Initially Ainsworth found that the greatest reduction in mortality was obtained by typhoid-paratyphoid vaccine. In a subsequent study, reported in a personal communication to H.C. Nauts, Ainsworth reported the following results:

Method: Typhoid-paratyphoid vaccine was used to compare with Coley Toxins (mixed toxins of *Streptococcus pyogenes* and *Serratia marcescens*, Johnston XV preparation) since previous data had shown that TAB is highly effective in reducing the radiation mortality in mice. The mice used were CF₁ females, 100 days old, weighing 19-24 grams. Total body X-irradiation was delivered from a 250 kv Westinghouse X-ray machine operated at 15 ma and a distance of 40 inches. Added filtration consisted of 0.5 mm Cu and 1 mm Al.

<u>Substance Injected</u>	<u>Amount Injected</u>	<u>No. Mice Injected</u>	<u>Picric Acid Mark</u>
Coley Toxins	0.1 ml	26	on head
Coley Toxins	0.05 ml	25	on back
TAB vaccine	0.1 ml	26	on tail
0.9% NaCl (saline)	0.1 ml	26	none

The mice received 700 r on the day following inoculation. The mice were then caged 8 to a cage - each cage containing two mice from each group. Death checks were made once a day for 30 days following irradiation. Deaths occurred between the ninth and seventeenth day. There was no observable difference in rate of death in the various cages.

SUMMARY OF MORTALITY

<u>Substance Injected</u>	<u>Amount Injected</u>	<u>Mortality*</u>	<u>%Mortality</u>
Coley Toxins	0.05 ml	0/25	0
Coley Toxins	0.1 ml	2/26	7.7

<u>Substance Injected</u>	<u>Amount Injected</u>	<u>Mortality*</u>	<u>%Mortality</u>
TAB Vaccine	0.1 ml	3/26	11.5
0.9% NaCl	0.1 ml	24/26	92.3

*No. dead/Total

This experiment suggests the importance of dosage, since a smaller dose of Coley toxins protected 100% of the mice, while with a larger dose 7.7% died.

D. Cole et al (1966) confirmed the radioprotective effects of the mixed bacterial toxins formerly known as Coley toxins.

Others who have studied the beneficial effect of bacterial endotoxins include Smith et al (1957), Hollcroft and Smith (1958) and Prigal (1969). The latter used a single emulsified injection of a lipopolysaccharide derived from *Escherichia coli* administered to mice during gestation yielding neonates that were highly resistant to lethal whole body radiation. The slow release of the emulsion eliminated the abortive and toxic effect of the LPS and prolonged its effective action. Smith et al. (1957) found that mice responded better to injections given 24 hours prior to irradiation, hamsters to injection immediately after irradiation. They stressed that time of injection is of primary importance. The effects are similar to those with bone marrow, and may be due to an advance in the recovery of natural defenses such as granulocytes.

Zweifach (1959) used *Escherichia coli* endotoxins and zymosan and reported that, whereas endotoxin engenders a broad pattern of resistance, zymosan confers a much more restricted adaptation, despite the fact that both involve stimulation of the phagocytic behavior of the reticuloendothelial system. If the RES of toxin treated rats is blocked by colloids, the x-rayed animals readily succumb.

It is of great importance to recognize that bacterial toxins not only protect the normal tissues against the deleterious effects of radiation but they potentiate the response of the tumor to radiation thus enabling one to use smaller doses of x-ray for effective treatment or to treat tumors which are usually radio-resistant (Chandler et al. 1968; Harcourt et al. 1968; Fowler, 1959-1969; Nauts, 1953-1970)

Other agents which can potentiate the effectiveness of radiation therapy include Actinomycin D, DMSO, Colchicine, estrogen, vasodilators and alphotocopherol. (Graham & Graham, 1960). Of special interest is the potentiation invoked by fever or heat as reported by many physicians including Rohdenburg (1921), Doub (1935), Crile (1961) and Nauts and Fowler (1969).

Beginning about 1952 considerable interest has been shown in the effectiveness of increased oxygenation of the tumor and its periphery on potentiating the radiation response of tumors. Hollcroft et al. (1952) reported that hydrogen peroxide injected intravenously or intradermally to tumor bearing animals immediately before irradiation increases the effect on tumor regression. Given after irradiation it did not significantly increase tumor damage. Others have used hyperbaric oxygen thus inducing more rapid regression of moderately radiosensitive tumors.

Howard-Flanders and Scott (1960) reviewed the subject based on a conference held in 1958. Gray (1961) noted that any slight increase in oxygen tension may be of importance in raising the radiosensitivity of the deeply hypoxic cancer foci.

Apparently bacterial toxin injections by their vasodilating effects, may increase the blood flow to tumor areas, thus significantly increasing the oxygenation of normally anoxic areas. This may be one way in which toxin therapy exerts its radio-potentiating effect upon the tumor. In this connection it may be of interest to note that few physicians are aware that injections of Coley toxins were used by H.J. Gray (1934) in treating thromboangiitis obliterans (with immediate vasodilation, healing of ulcerated gangrenous lesions and lasting cure).

It would seem that bacterial toxin injections may prove to be the easiest, cheapest and most effective way of protecting the host and enhancing the effectiveness of radiation therapy. Timing is of great importance in securing these beneficial effects.

Dastre (1893) was the first to describe the fibrinolytic system in human blood but this interesting phenomenon fell into semi-obscurity as so often is the case with new discoveries (Ambrus, 1960). Evidence is accumulating that this system is one of the fundamental processes in physiology. (Askup, 1956)

The suggestion that fibrinolysin might be of value in the treatment of cancer is of recent origin. However proteolytic enzymes were used from time to time on cancer patients for nearly two hundred years. Crude pepsin was used locally; especially in the late 19th century. (Tanchou, 1844) Some of the reported successes may have been due to the fact that erysipelas developed at the site of these injections. (Lussana, 1869)

Beginning in 1906 trypsin and pancreatic extracts were used on a considerable number of patients in the next six years in Denmark, England, France, Germany, Italy, and the United States. Shaw McKenzie (1907, 1909) was the originator of the method in London (Ligertwood, 1907). At first he gave these pancreatic preparations by mouth then by injection, in the treatment of inoperable cancer patients. In 1909 his animal experiments were inconclusive. Woglom in citing this work stated that "accelerated lipoclastic activity may be a possible protective process against cancer. Beard (1906) also claimed to be the first to originate the method. He advised that after four weeks of trypsin injections amylopsin should then be used (40 minims daily).

Among those who reported successful results were some without microscopic confirmation of diagnosis. Others did have histologic proof. These include Morton (1906), Hudson (1907), Goeth (1907), Alcindor (1908), Durodié & Duborg (1909). Alcindor believed that trypsin must be injected into the tumor and that therefore cancer of the internal organs could not be successfully treated. He reported it to be of considerable value in cancer of the uterine cervix, rodent ulcer and epithelioma. He thought amylopsin was of no benefit.

Other reported negative results: Hald (1907), Weinstein (1908), Lambille (1907, 1909), Bainbridge (1907, 1909). The latter stated in 1907 that "much of the trypsin put on the market for cancer injections is absolutely devoid of digestive

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properties that is, is not trypsin at all but only glycerine and water." He believed that this may have been the cause of some of the unsatisfactory results. Hald also discussed the comparative strength of various preparations then in use. Campbell (1907) stated: "Considering the natural and comparative immunity of the duodenum and small intestine to cancer, it would appear that the theoretical treatment of inoperable cancer by preparations of the pancreas. . . is readily supported. Von Bergmann stated (1904) that cancer of the stomach stops abruptly at the pylorus, and that the small intestine is rarely the site of cancer and that cancer of the colon and rectum for the most part increases in frequency the further the distance from the duodenum." In 10537 cases of the alimentary tract Von Bergmann found 4288 involving the stomach, only 20 in the small intestine, 224 in the colon and 1204 in the rectum.

The most extensive series (100 cases) was published by Bainbridge (1909). He summarized his experience as follows: that the internal medication with pancreatic extracts aids digestion and increases elimination. That when these extracts are applied locally they clear the ulcerating surface by removing organisms, thus aiding in diminishing the absorption of their products. That this regime, by increasing resistance may in some cases decrease the rapidity of the malignant process. That in some cases injections of trypsin seems to cause more rapid disintegration of cancer tissue, i.e. "to liquefy it". That while it may accelerate the breaking down in the center of the tumor mass, the periphery actively grows. When injected into the tumor itself this disintegration is more marked. That because of its tendency to cause necrosis it may cause fatal hemorrhage, thus hastening death. He added that injections of amylopsin seemed to diminish cachexia in some cases and in a certain number hemoglobin increased 5-12% in the first few weeks of trypsin treatment. He concluded, however, that this treatment does not prevent metastasis or cure cancer.

In this connection it is of interest to remember that prior to 1850 cancer was sometimes empirically treated by the application of leeches or maggots. It

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is now known that maggots secrete trypsin. A substance called Hirudin was excreted from the salivary gland of leeches which is an anticoagulant. Injections of Hirudin caused hemorrhages, especially in rapidly growing tissues such as tumors. (Fleischer, 1914). Lewin (1912) gave 58 references to the use of "gastric juices" in his review of the treatment of inoperable cancer.

More recently a few investigators in France and Germany such as Raab (1935) have reported that intravenous injections of purified trypsin had a therapeutic effect in cancer. Cliffton (1969) tried to confirm this but was unable to do so.

Connell (1935) reported on the effects of injections of proteolytic enzymes obtained from *Clostridium histolyticus* which he called ensols. Gye (1935) was unable to confirm Connell's work on mice: "in no case was the growth of a tumor checked or affected in any way".

Parker et al. (1947) injected spores of *Clostridia histolyticus* directly into a rapidly growing transplanted fibrosarcoma in mice, and with the administration of histolyticus antitoxin prolonged survival time of some animals. Histolyticus toxin injected directly into a tumor caused marked regression.

It is evident that none of the above proteolytic substances proved of great use in the treatment of cancer in man.

Sproul (1938) was the first to report on the frequency of association of multiple venous thromboses in patients with carcinoma of the body or tail of the pancreas. He stated that they were found in 31% of all autopsied cases at Presbyterian Hospital. This thesis has been proved many times since. (Hoer and Harper, 1957; Pelner, 1963). Jennings and Russell (1948) in discussing this stated: "In all cases of disseminated phlebothrombosis, attention should be directed to the possible existence of carcinoma and a careful search made for signs and symptoms pointing to its identification."

Mucin can be a resistance lowering substance not only in connection with infections (Olitski, 1948), but in neoplasms. Its coating of bacteria or tumor cells prevents phagocytosis and other immune mechanisms. Currie and Bagshawe (1967) reported that the protective coat - mucin which is present on the surface of tro-

phoblasts and cancer cells is known to confer a high electronegative surface charge. Since lymphocytes also carry a negative charge these trophoblasts and tumor cells escape attack by lymphocytes in vivo by electrochemical repulsion. Trypsin removes these substances and thus renders these cells more vulnerable to the lymphocytes.

Trauma is one of the factors which can inhibit fibrinolysis and which is implicated with tumor growth and spread. This includes accidental injuries and surgical trauma.

Briggs et al. (1947) reported that strenuous exercise and the injection of adrenaline produce fibrinolytic activity in the blood of normal persons: "It seems probably that the fibrinolysis associated with fear, trauma and some pathological states follows indirectly the stimulation of adrenalin secretion. Fibrinolysis. . . appears to be a component of the initial phase of the alarm reaction. R.W. Smith et al. (1950) discussed the influence of ACTH and cortisone on certain factors of blood coagulation and noted that in general the alarm reaction decreases clotting time.

MacFarlane (1948) noted that fibrinolysis is increased after wet cupping and occurs in all conditions which lead to the secretion of adrenaline, i.e. trauma, fear or severe exercise.

Fisher and Fisher (1959) demonstrated the significant activation or spread of tumor following trauma in experimental animals.

Cliffton (1969) reported that surgical trauma in rats results in an increase in fibrinogen and fibrinolysin inhibitor levels, maximum at about five days, and that the incidence of metastases peaks at the same time after trauma.

STREPTOCOCCAL ENZYMES: About 1933 Tilleff and his associates began reporting that ~~broth~~ cultures of hemolytic streptococci derived from patients were capable of rapidly liquefying human fibrin clot. They found that the degree of activity of the filtrates parallels the activity of the whole broth cultures sufficiently closely to indicate that large amounts of the fibrinolytic substance are freely excreted into the surrounding medium and pass readily through Berkefeld, Seitz, or Chamberland filters. However, normal rabbit fibrin clot was totally resistant to dissolu-

tion when tested by these investigators.

Tillett and Sherry (1949) noted the high degree of activity of the streptococcal lytic system in the presence of normal human blood as contrasted with its inaction or delayed effect when tested with the blood of various animals with the exception of monkeys. The existence of this difference prevented most in vivo experimental studies on animals and limited them to observations on patients.

Tillett et al. (1934) reported that following acute hemolytic streptococcal infections patients developed resistance to fibrinolysis.

By 1957 greatly purified preparations of streptokinase (the fibrinolytic exotoxin derived from certain strains of hemolytic streptococci) were available and this greatly diminished toxicity. Systemic fibrinolysis could thus be induced in men by infusion of these preparations unprotected by reaction-suppressing drugs. They were asymptomatic.

J.M. Miller et al. (1955, 1956) reported: "The course of inflammation is greatly influenced by the extracellular products or enzymes produced by the gram positive bacteria. Hemolytic streptococci produce streptokinase, streptodornase (a group of depolymerases), ribonuclease, proteinase, hyaluronidase, streptolysin O and streptolysin S. Pathogenic strains of staphylococci produce staphylokinase and hyaluronidase. *Clostridium welchii* produce alfa toxin or lecithinase, collagenase and hyaluronidase. Streptokinase and staphylokinase, by causing fibrinolysis, may spread infection. Coagulase clots blood plasma and the fibrin deposited about the staphylococci may prevent phagocytosis. The hyaluronidase may influence the dissemination of bacteria or their toxins. The production of hyaluronidase is apparently not related to the virulence of streptococci in man. To obtain good results with intramuscular injections of streptokinase the area must have good circulation where necrosis of tissue has occurred. If an abscess has formed, incision and provision for drainage must be made. The local application of Varidase and Tryptar is valuable: a) they liquefy viscous barriers and permit more efficient action by antibiotics and easier removal of the debris. b) They also stimulate the appearance of normal leukocytes which can move freely to undertake phagocytosis. c) They promote the growth of

granulation tissue. In reporting on his clinical experience with injections of streptokinase (Varidase) he stated that such treatment activates the plasminogen in the euglobulin fraction of the blood to plasmin. Plasmin causes lysis of fibrin. Fibrinolysis thus causes a more efficient circulation and resorption of edema fluid. With paths of delivery more open, phagocytes, humoral antibodies and drugs can reach the target tissue in greater concentration and act more effectively.

Miller's work was directed to the control of injections and edema in non-cancerous patients, but it is now becoming apparent that one of the main reasons streptococcal injections were responsible for so many of the so-called spontaneous regressions of cancer was because of these enzymes which decreased the likelihood of metastases by their fibrinolytic effect, increased the permeability of the tissues so that the phagocytes and humoral antibodies to the tumor could reach the tumor cells and so that the necrotic tumor tissue resulting from this process could be more speedily absorbed.

An editorial in the J.A.M.A. in 1907 on spontaneous healing of cancer was prompted by the paper read by Czerny (1907) in which he cited his own experiences including a case of mammary carcinoma which had recurred. Following surgical removal of this recurrence the patient developed an erysipelas infection. She remained well and free from further evidence of disease 20 years later. Czerny quoted with evident approval the statement of Lomer (regarding recoveries after palliative procedures), "that a favorable outcome is much more likely to follow local treatment with the thermocautery or with chemical caustics than incomplete operations with the knife." (Lomer, 1903) The editorial concluded as follows: "We can imagine that the checking of metastatic growth could result from a process of self immunization. During the operative manipulation of the primary growth considerable quantities of cancerous material may be forced in to the circulation and the results might either be (1) a widespread dissemination of the disease, which is frequently observed, or (2) in case the resistance of the body were sufficient these cells would be destroyed and in the process cause the formation of antibodies sufficient to enable the in-

dividual to overcome the secondary growths which had already obtained a foothold."

Terranova and Chiossone (1952) were apparently the first to use anticoagulants in animals in order to decrease metastases after intravascular injection of tumor cells. At about the same time Agostino et al. (1952) reported that anticoagulants such as Warfarin or heparin or agents which lyse clots such as human fibrinolysin, can decrease the incidence of metastases of the Walker 256 carcinoma. Cliffton and Grossi (1956) reported this effect with the Brown Pearce carcinoma and the V2 carcinoma in rabbits.

These authors found that rats made hyperlipemic by being fed a high fat diet for 21 days, showed inhibition of fibrinolysis. Metastases in the lungs occurred much more frequently in the hyperlipemic than in the control rats, and larger numbers of metastases were seen in the individual hyperlipemic animals (Cliffton et al. 1961). Hahn (1943) had reported that heparin causes rapid clearing of lipemia following a fatty meal.

Eichenberger et al. (1954) reported that fibrinolysin had been activated with Pyrexal, a highly purified lipopolysaccharide derived from *Salmonella abortus equi*. They found that even after a small only slightly pyrogenic dose of Pyrexal distinct fibrinolysis occurred in human volunteers (Eichenberger et al. 1955). Stamm and Eichenberger (1958) found that Pyrexal could be used effectively as a prophylactic to prevent emboli in cases of venous thromboses, even in patients where hemorrhages contra-indicated the use of anticoagulants.

Horder et al. (1958) reported that injections of Pyrexal greatly increased fibrinolysin in mice. However, if phenylbutazone was given (500 mg) no fibrinolysin occurred. At a German Study Group for Blood Coagulation held in 1967 in Munich, Marx noted that inhibition of fibrinolysis increases the tendency to metastases. If patients with carcinoma are given anticoagulants, especially heparin, a fat-poor diet and hot baths, fewer deaths occur on such long term therapy than would be expected. Gastbar stated at this conference that cancer cells circulating in the blood stream are more viscid and adhere to the endothelial lining thus causing thrombosis. They

soon penetrate the endothelium and begin to multiply. Tumor cells have a fibrin coating, and their fibrinogen content is considerably higher than that of normal cells. When heparin is administered, the tumor cells can no longer adhere to the endothelium and quickly perish. Survival time can thus be prolonged and metastases prevented.

Sokol et al. (1958) reported their experiences in treating thrombosis with fibrinolysin (plasmin) prepared from human and bovine plasma. A total of 114 infusions of fibrinolysin were given to 37 volunteer patients, most of whom had incurable cancer. Thirteen episodes of acute thrombophlebitis, occurring in 10 of these patients, were treated. In five of the eight patients in whom the age of the thrombus was three days or less, complete resolution was obtained. When improvement did occur, the pattern of response was fairly uniform: pain was relieved in 24 hours, color improved and tenderness disappeared shortly thereafter, and edema disappeared within a few days. He described the results, which were sometimes striking, illustrated in 14 case histories. Fibrinolysin was ineffective when begun a week or more after the thrombosis developed, and it did not prevent the formation of fresh thrombi. They suggested the simultaneous administration of anticoagulants and fibrinolysin in the management of acute thromboses.

Ambrus et al. (1960) reported the further experiences of this group at Roswell Park, on a series of 196 patients treated with various types of fibrinolytic enzyme preparations. Of 538 intravenous and/or intra-arterial infusions, hemorrhage occurred in 12 cases, pulmonary embolism in two. Pyrogenic side effects were common with earlier preparations but occurred only four times in 385 treatments with newer more purified preparations. With four to eight hours infusions, decrease in factors of the blood clotting system was never of sufficient magnitude to be of clinical significance. Rapid intravenous injection resulted in more pronounced changes.

Retreatment with streptokinase or streptokinase-activated plasmin three weeks after an initial course of therapy resulted in anaphylactoid reactions in two of

three patients. Retreatment with urokinase-activated plasmin caused no side effects and did not result in decreased therapeutic activity in 12 cases. They concluded that therapeutic results in the groups of patients treated with fibrinolysin were superior to those in the untreated group or groups treated with anticoagulants.

Cliffton et al. (1961) found that patients with moderately advanced cancer have high fibrinogen and fibrinolysin inhibitor levels. Operative procedures result in a rise in fibrinogen and fibrinolysin inhibitors. The rapid increase in metastases which sometimes occurs postoperatively may be related to this mechanism. They suggested that clotting mechanisms be evaluated in all cancer patients. In another report in 1961 they reported that injections of fibrinolysin or heparin resulted in a marked diminution in the number of tumor cells in the blood of rats with unresectable tumors and a decrease in the number of cells at the time of manipulation in animals with resectable and unresectable tumors. There was a marked decrease in the number of tumors in the mice so treated. Cliffton and Agostino (1963) found that heparin, especially when prolonged (seven days) reduces the incidence of metastases of the V₂ carcinoma in rabbits.

Cliffton et al. (1962) reported: "It has been shown repeatedly that patients bearing malignant tumors have very high fibrinogen and fibrinolysin inhibitor levels. Both conditions will lead to an increased tendency to fibrin formation and may be a factor in the development of metastases. Furthermore, at the time of operation, it is possible that tumor cells freed into the circulation may adhere to the endothelium in a fibrin thrombus and ultimately produce metastases. If this could be prevented by the use of a fibrinolytic agent or by anticoagulants, then the removal of a resectable tumor which happened to spill cells at the time of operation would be more likely to result in a cure. Variations in the clotting mechanism at the time of surgery and in the immediate post-operative period are well recognized. In a few cases, excessive hemorrhage occurs due to fibrinolysis or failure of coagulation. More frequently thrombosis occurs fairly rapidly after surgery. It may be that control of these factors will be found to be important in the rate of spread

of the disease."

When fibrinolysin was combined with other forms of treatment the results were even more convincing. When irradiated tumor cells (1000 r) are injected intravenously the incidence of pulmonary metastases is the same as with non-irradiated cells. However, when fibrinolysin is infused before the tumor cell injection, the incidence is reduced from 87% to 56%. With the V₂ carcinoma the incidence of metastases with irradiation only was reduced from 100% to 90%. However with a single injection of fibrinolysin the incidence of metastases was reduced from 100% to 65% in the non-irradiated and from 90% to 35% with the irradiated cells. When fibrinolysin was infused for seven days beginning just before the tumor cells were infused, no metastases developed.

Agostino and Cliffton (1963) confirmed these results in an experiment more closely resembling a clinical situation, the spill of tumor cells at resection. They used a cecal tumor with Walker 256 cancer in rats. The tumor was explored at a resectable stage, massaged and resected. Liver metastases were found in 34% of the control and 19% of the fibrinolysin-treated animals (one injection prior to the massage). At post mortem 26% of the fibrinolysin-treated animals were free of cancer.

Fisher and Fisher (1961, 1967) confirmed these findings with fibrinolysin and metastases of the Walker 256 carcinosarcoma, though they thought more than one infusion was necessary. They also found that it was most effective when given prior to the tumor cells. Rudenstam (1967) found that results varied with the type of tumor. He reported no significant improvement with the more malignant rapidly metastasizing tumors. He also suggested that there might be an increase in metastases with fibrinolysin if the primary tumor is not removed.

Wood (1964) demonstrated that infused tumor cells became fixed in a clump of fibrin and then permeated the vascular wall and reached the extravascular space and grew. Locally injected fibrinolysin reversed this process.

Walton (1952) studied a new synthetic anticoagulant (low molecular weight dex-

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tran sulphate) which like heparin, do not form insoluble complexes with the plasma proteins, under physiological conditions. For this reason apparently these dextran sulphates are no more toxic than heparin yet show quantitatively similar behavior as anticoagulants, making it possible to employ them as heparin substitutes. High molecular weight dextran sulphates do form precipitates.

Ryan et al. (1968) reported that continuous anticoagulation by Warfarin sodium to maintain a prothrombin time of twicenormal in mice reduced spontaneous metastases from transplanted tumors from 83% in the controls to 8% in the treated mice. Treatment also retarded the growth of the primary. Length of survival was unaffected.

Bale et al. (1960) reported that rat fibrin prepared from immunized rabbits and made radioactive by in vitro coupling with I^{131} localized with considerable specificity in several transplantable rat tumors after intravenous injection into rats bearing these tumors. Intravenous doses of 1.22 to 4.13 mc. of I^{131} attached to rat fibrin antibody, injected into rats bearing the transmissible Murphy-Sturm lymphosarcoma after the tumors had grown to 2-3 gm. in weight, consistently resulted in rapid and permanent regression of these tumors.

Sahli (1885) found a tryptic enzyme in urine. Macfarlane and Pilling (1947) rediscovered the tryptic activity of urine and reported that fibrinogen, fibrin, albumin and casein were digested and suggested some relation to the plasmin in the blood. Several other investigators working independently made it clear that the activity was caused by an activation of plasminogen (Astrup 1952, 1956).

Sobel et al. (1952) reported the concentration and partial purification of an "urokinase".

Other investigators studied the fibrinolytic activity of tissues. Astrup (1956) worked out a quantitative method for estimating the plasminogen activator in tissues.

SPONTANEOUS FIBRINOLYTIC ACTIVITY:

Fibrinolytic activity occurs spontaneously in blood and other fluids in the organism. (Astrup, 1956) While urine contains a high activity, caused by an activation of plasminogen, blood normally contains no (or very slight) activity; but

under certain conditions a considerable activity can be found. This occurs in sudden death, in states of anxiety, after adrenaline injection and in a number of conditions relating to shock. Death from asphyxia is also associated with high fibrinolytic activity.

The fibrinolytic activity produced by adrenaline or exercise disappears very rapidly from the blood.

Astrup in a comprehensive review on fibrinolysis (1956) stated that the long term treatment with anticoagulants of the dicoumarol type, now in general use against thrombo-embolism, decreases the ability to form new clots and prevents the growth and spread of the primary deposits. However, the removal of existing deposits depends completely upon the natural thrombolytic processes of the organism. Increasing the patient's fibrinolytic activity constitutes a rational therapeutic measure. The most direct approach is the intravenous administration of potent fibrinolytic enzymes. This clinical possibility aroused great interest in the preparation of purified plasmin. A homologous protein plasmin of human origin has evident advantages over streptokinase and trypsin. Staphylokinase and dog fibrinolysin (plasmin) given to dogs intravenously produced a considerable fall in antiplasmin and disappearance of fibrinogen with production of hemorrhagic areas in the organs. Plasminogen decreased in concentration only when staphylokinase was injected and not when the active plasmin was used. Tillett was the first to use streptokinase intravenously in humans. Streptokinase has been used intrathecally and in the prevention of adhesions. Because of species specificity of the proteins involved and the large doses needed it appears improbable that any animal blood can be used as a source of raw material for this important compound.

Extensive studies by Astrup (1952, 1956) have shown that fluids in the organism (i.e. urine, milk, tears, and seminal fluid) contain fibrinolytic systems which assist in the removal of fibrin clots in the excretory ducts.

The simultaneous presence in the blood of active, activating and inhibitory agents presents a puzzling problem. One of the obstacles is the fact that many more

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compounds are involved in the reactions than was originally imagined 20 years ago. This and the difficulties involved in investigating a rather slow process, in contrast to the easily observable rapid process of blood clotting, have been the main causes of the previous slow progress in studying the fibrinolytic process (Astrup, 1956).

THE COAGULATIVE PROPERTIES OF CANCER CELLS:

In Dublin O'Meara, Jackson and Thornes (1958-1969) became interested in the coagulative properties of cancer cells. O'Meara & Jackson (1958) observed that fibrin is deposited continuously on the surface of cancer cells. As it is laid down in the periphery of neoplasms a network is generated along which cancer cells can grow. O'Meara (1960) suggested that fibrin deposited on tumor cells may serve as an important nutrient. The level of cancer coagulative factor (CCF), fibrinolytic enzymes and their activators in tumors and the surrounding normal tissue may influence the rate and invasiveness of tumor growth.

In seeking means of inhibiting CCF, Thornes and Sheehan (1966) found that this could be accomplished in vitro by human plasmin, protamine sulfate, protease of *Aspergillus oryzae*, fucidin and dextran. They found plasmin was the most active of the inhibitors of CCF. O'Brien et al. (1968) reported that Protease I (a fibrinolytic enzyme derived from *Aspergillus oryzae*) inhibited thromboplastin and anti-in vitro, and this antiplasmin activity plasmin activity is potentiated in vitro by human thromboplastin. The in vivo effects of this enzyme were examined in cancer patients, since thromboplastin activity is raised in cancer tissue, and such patients have increased levels of antiplasmin. Thirteen patients with cancer and one with occlusive vascular disease were given one or more infusions of protease. Side effects were mild and transient, except for pathological fibrinolysis (in three cases on a high dose) and a coagulative defect in one case. Subjective improvement and diminution of pain was noted but they cautioned that it was too early to judge the final effects of such therapy. They noted that no patient deteriorated as an immediate result of therapy and stated that they were encouraged by the improvement in a case of advancing multiple myelo-

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ma with paraplegia. They suggested that the fibrinolytic effect of protease should be of value in removal of fibrin from malignant tumors. The mobility of the cancer cell may be inhibited and the cell rendered more vulnerable to cytotoxic therapy (or to humoral defenses). O'Meara (1963, 1964) has reported successful results in the treatment of cancer with fibrinolysin and other inhibitors.

Thornes (1967) reported on fibrinogen and the interstitial behavior of cancer stating that further studies confirmed the conversion of fibrinogen to fibrin in dilute plasma at pH 6.5 by a cancer coagulative factor from human cancer cells. He suggested that CCF is similar to known thromboplastins.

In the cancer host the fibrinolytic system is suppressed by the rapid production of inhibitors (antiplasmins) in response to mild stimulation. The action of the CCF can be blocked in the human and rabbits by the dicoumarol type of anticoagulants. In the dicoumarol treated rabbits preliminary experiments with V₂ carcinoma cells revealed that the motility of the cancer cells was decreased and numerous cells died. He discussed the possibility that these changes may be related to a decrease in fibrinogen or fibrin deposition. (Thornes 1967, 1968) In a further study, Thornes et al. (1968) reported on the effects of sodium warfarin therapy on the behavior of normal and V₂ carcinoma cells in the rabbit ear chamber, using time-lapse cinemicrography. No alterations of cellular motility occurred in the control rabbits. In the warfarin-treated animals, the locomotion of cancer cells was selectively inhibited for 20 days whereas the motility of granulocytes, lymphocytes and macrophages and V₂ cancer cells was selectively inhibited for no time at all. In two of the three treated rabbits resistance to warfarin developed, motility of tumor cells returned and dissemination of cancer proceeded. One of the treated animals remained sensitive to warfarin therapy, and was free of cancer at autopsy. All other rabbits developed cancer. Whether the effects of warfarin on motility of malignant cells were exerted indirectly through the coagulation mechanism or indirectly on the cancer cells is uncertain.

In this connection it is of interest to consider the cytotoxic effects of living hemolytic streptococci reported by Havas et al. (1963) using phase micro-

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scopy and in vivo implantation into mice. The effects produced by *Streptococcus pyogenes* strains were compared with those of *Serratia marcescens*, *Sarcina lutea* and *Streptococcus faecalis*. Three of eight strains of streptococci were highly effective against ascites tumor cells (Sarcoma 37 and Krebs 2 carcinoma) resulting in a reduced number of tumor takes and reduction of tumor sizes, whereas *Sarcina lutea*, *S. marcescens* and *Streptococcus faecalis* were only partially effective in damaging tumor cells after in vitro incubation. When streptococci were added to the tumor cells their motility ceased rather abruptly and within about 30 minutes the tumor cells were destroyed as shown by phase photomicroscopy.

Baird (1968 , p. 173-174) in a monograph entitled The Human Body and Bacteria, described 40 years' experience in treating various conditions from allergies to rheumatic and collagen diseases with periodic courses of bacterial ^{injections of} products. He discussed cancer and immunity as follows: "It should be of interest to those doing research concerning cancer that of the hundreds of persons of all ages and both sexes who have had a course of bacterial antigen-antibody in large doses as prescribed here, none, to my knowledge, developed cancer afterwards.. . . Suppose some cancer cells are developing but the body is barely able to deal with them, might it not be that the stimulation of sufficient bacterial antigen would turn the battle in favor of the body.. . ."

Baird considered only the antibody response to such treatment. We must also consider its effect on fibrinolysis.

In 1969 Thornes reported again on his results with anticoagulant therapy in cancer patients. At this time he stated: "There has been a surprising lack of interest in the mechanisms of spread of cancer and the application of their control to human cancer therapy. Since 1952 (Terranova and Chiossone) anticoagulants have been used in animal experiments to decrease metastases after intravascular injection of cancer cells. Human plasmin was first used in 1956 by Clifton and Grossi to decrease the intravascular spread of tumor in rabbits."

In reporting the clinical results Thornes stated: "There are few problems

arising from anticoagulant therapy and patients generally enjoyed the extra attention required by prothrombin control. Hemorrhage was less than expected but one cerebral hemorrhage. Two further fatal case of multiple myeloma with hypertension died from a cerebral hemorrhages occurred both in patients with cerebral secondaries from carcinoma of the breast. Hemoptysis occurred in three cases of carcinoma of the lung. Vaginal bleeding occurred in a case of carcinoma of the uterus. One case of Hodgkin's disease had rectal bleeding. . . .The rectal patient who developed hematuria had an inoperable adenocarcinoma of the rectum, aged 52 years with a rectovaginal fistula and bladder involvement. She refused pelvic exenteration and was treated by colostomy, protamine, streptokinase and anticoagulants. She was examined under anesthesia three times . . .by a gynecologist and a surgeon and finally three months later her tumor had regressed sufficiently to allow palliative excision of the main tumor mass with conservation of the vagina. Anticoagulants were continued for a further two years and then stopped. She is alive and clinically tumor free five years later." (Thornes, 1969)

"A case of Hodgkin's disease of three years' duration with an enlarged liver (8 cm.) unresponsive to cyclophosphamide had a prothrombin time of 24 seconds (control 16 seconds). Dindevan therapy (25 mg. daily) increased the prothrombin time to 35-40 seconds. Cyclophosphamide was continued and over the next two weeks Dindevan dosage had to be gradually increased to 100 mg. daily to maintain a prothrombin time of 30 seconds. The liver decreased in size to just below the costal margin and cyclophosphamide was stopped. During subsequent months each time liver enlargement occurred anticoagulant requirement decreased. A course of cyclophosphamide reduced the liver size and increased the tolerance again to the anticoagulant. After three months this stopped and the patient remained static on a dose of 50-75 mg. of Dindevan for three years. She still requires occasional cytotoxic therapy and steroids."

Thornes noted that in seven patients the response to cytotoxic therapy appears to have been enhanced. Four of these cases (two lymphomas, one carcinoma of the

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breast and one of the ovary) have been maintained for more than a year on anticoagulants alone. The other three patients have stopped all therapy after two years' response: carcinoma of the rectum, ovary and a rhabdomyosarcoma. The latter was treated by repeated excision, deep x-ray therapy and cytotoxic therapy but recurred until anticoagulants were started.

Lymphoma and carcinoma of the ovary appeared to benefit most from adjuvant coagulant therapy and Thornes felt such cases might provide a definite answer in a controlled clinical trial.

One early case of Hodgkin's disease is of special interest: There was bilateral involvement of the cervical ^{lymph} nodes, diagnosed by excision biopsy of the largest nodes (2 x 2 cm.) on one side. Before being referred for x-ray therapy the patient was given anticoagulant therapy with Sinthrome. After two weeks the contralateral nodes (1 x 1 cm.) to the excised area became tender with slight increase in size, remained so for one week, then regressed completely. No x-ray therapy was given and anticoagulant ~~and anti-inflammatory~~ therapy has been continued for about two years without sign of recurrence.

In the discussion Thornes stated that in this trial one got the impression that patients feel better while on anticoagulants and die more rapidly in the terminal stages. "Human tumors form their own fibrin stroma, tumor cells in culture can be protected by fibrin from cytotoxic substances, and cancer cells in vivo stop moving if prothrombin levels are lowered for five days by warfarin anticoagulant. He asks: "Does anticoagulant therapy, therefore, enable host factors or cytotoxic agents to get at the tumor cell better? We do not know but at least it appears to be acceptable to patients and reasonably safe in a controlled trial.

Enhanced fibrinolytic activity has been demonstrated to occur in the blood of almost all patients subjected to electroshock and pyrogen injections and in male subjects following severe exercise. A less consistent response has been shown to occur following epinephrine, acetylcholine and ischemia (Sherry et al., 1959).

The optimal biochemical conditions to effect consistent and reproducible clot

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present and one of the many) have been maintained for more than a year on active surveillance. The other three patients have stopped all therapy after two years response. Complications of the lesions, mainly a rhinomyeloma. The latter was treated by repeated excision, deep x-ray therapy and cyclophosphamide therapy but retained until antitumor chemotherapy started.

Lymphoma and carcinoma of the ovary appeared in patients most from adjuvant chemotherapy and hormone therapy. Such cases might provide a definite answer in a controlled clinical trial.

One early case of Hodgkin's disease is of special interest. There was bilateral involvement of the cervical nodes, diagnosed by excision biopsy of the left axillary node (2 x 2 cm) on one side. Before being treated for x-ray therapy the patient was given antitumor therapy with 4000 rads. After two years the bilateral nodes (2 x 2 cm) in the axilla were again excised with a 10% increase in size, remained so for one week, then regressed completely. No x-ray therapy was given and antitumor chemotherapy has been continued for about two years without sign of recurrence.

In the discussion Johnson stated that in this trial one of the important facts was that both sides of the antitumor therapy were given equally in the bilateral cases. "When there is bilateral disease, cancer cells in bilateral nodes are protected by fixation from cytotoxic substances, and cancer cells in vivo stop moving. It is probable that the low level of fixation for five days by x-rays in lymphoma and carcinoma is not sufficient therapy, therefore, should not be taken as evidence to get at the true cell pattern. We do not know but at least it appears to be acceptable to patients and reasonably safe in a controlled trial.

Enhanced fibroblastic activity has been demonstrated in nodes in the nodes of almost all patients subjected to radiotherapy and systemic injections and in some subjects following surgery. A less consistent response has been shown to occur following epinephrine, norepinephrine and testosterone. (Berry et al. 1974).

The optimal biochemical conditions to select consistent and reproducible clon-

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lysis in man and prevent clot formation are created when streptokinase is infused to produce small amounts of plasmin and free streptokinase or activator in vivo (Johnson & McCarty, 1960).

The administration of a variety of nonfibrinolytic, non-enzymatic substances can induce fibrinolysis in man. The most potent materials of this type known at present are purified protein-free pyrogens. Their action after intravenous injection on the human fibrinolytic system, on some of its components and on the clotting system was studied by Von Kaulla (1958) in 67 individuals. He used a .2 microgram dose of the lipopolysaccharide derived from *Salmonella abortus equi* or 300 micrograms of *Escherichia coli* (acetylated form) ^{to} induce very marked fibrinolysis 60-90 minutes after intravenous injection. This lasts 60-240 minutes in man. At peak activity (105 minutes) clots dissolve in less than three hours. Concomitant treatment with antipyretics does not diminish the fibrinolytic response. Repeated daily injections gradually become less effective in inducing fibrinolysis. He observed encouraging results with induced fibrinolysis in patients with thrombophlebitis.

Clinical trials in this country by Clifton (1969) have been limited to patients receiving irradiation therapy for cancer of the lung. Only one group has been large enough or followed long enough to suggest any response. This is the group with superior vena cava obstruction secondary to lung cancer. The incidence of clinical metastasis has been quite low.

In all reports the treated series have been compared with estimated cancer incidence. In general the cancer incidence rate has been similar, but the death rate has been less in the treated patients. Michaels (1964) made a retrospective clinical study of the effects of long term oral anticoagulant treatment on cancer incidence in patients with thromboembolic disease. He found the incidence much less in the treated group and survival was better: only one death although the expected rate was eight. He concluded that anticoagulant therapy may alter the natural history of cancer.

Up to 1969 no one had reported on the effect of anticoagulants during opera-

tion on the incidence of metastases. Cliffton (1969) has attempted to do this with heparin, but significant data is not yet available.

A group in Copenhagen, Amris et al. (1963-1964) and Larsen et al. (1964) used porcine plasmin over a period of weeks to 11 cancer patients. They reported subjective improvement in six and objective improvement in five; regression of tumor occurred in four of these patients. Dahl (1966) using the same agent reported no improvement in his patients.

O'Meara (1970) noted that fibrinolysins cause the liberation of vast numbers of cancer cells from tumors and these flood the blood vessels leading from the neoplasm. He suggested that these agents may lead to widespread dissemination of the disease. It would seem that this might occur if immunosuppressive drugs had been administered prior to fibrinolysins, but that if host stimulating agents had been used, the malignant cells might rapidly be destroyed in the blood stream, thus acting as a further stimulus to immunity, i.e. an autogenous cancer vaccine produced in the host.

As to what can be done for patients who have developed lymphedema or acute thrombophlebitis as a result of radical mastectomy, or to prevent such complications, Evans (1961) stated: "Ideally, all patients who have radical mastectomies should have prophylactic anti-coagulation treatment with acenocoumearol, beginning three days after operation, to be controlled." Evans found swollen arms in 83% of the patients with grade II to IV carcinoma. Venography invariably showed an obstructed brachial or axillary vein. The venous channel cleared in only 1 of 13 patients with acenocoumarol, but in 5 of 10 on fibrinolysin (actase), as proved by venogram. He concluded: "Whatever the mechanism of intravascular dissolution of the clot may be, from the clinicians point of view, fibrinolysin does seem to be an effective agent."

The first four patients treated with fibrinolysin (actase) had severe pyrogenic reactions with temperatures of 101.8°-104°F. with the newer product, supposedly free of pyrogens, one had a fever of 102°F. and a second in whom a good result was obtained had no fever.

Salsali and Cliffton (1965) suggested that because of the high incidence of thrombosis (superior vena caval obstruction) with carcinoma of the lung, anticoagulant or fibrinolytic therapy or both might be of value as an adjunct to radiation and chemotherapy. They added that promising results had already been obtained using fibrinolysis therapy with or before irradiation.

Others have used urokinase, an enzymatic fibrinolytic activation that converts plasminogen to plasmin, and which is found as a trace in human urine. No deaths occurred in 10 patients with pulmonary embolism as contrasted to the high mortality rate with embolectomy in a series reported by Sautler in Wisconsin.

It is now recognized that extensive activation of the fibrinolytic system occurs in patients with severe febrile episodes during surgery. Possibly some of the spontaneous regressions reported to have occurred following episodes of hemorrhage may have been due to unusually active fibrinolysis in such patients.

Suzman (1961) reported at a symposium on anticoagulant therapy that cancer was found in only six patients treated with anticoagulants for a prolonged period as

compared with 31 of those not on anticoagulants.

Of interest to surgeons is the study by R.E. Gross and Villavicencio (1962) who reported that by using human fibrinolysin adhesions could be prevented in 100% of the dogs that received large doses of the enzyme intravenously during surgery designed to create adhesions. However, peritoneal adhesions developed in all animals given the enzyme intraperitoneally. They stressed that the intravenous route was the key to the solution of the problem.

Michaels (1964) reported on a retrospective clinical study of the effects of long term anticoagulant treatment on cancer development in patients with thrombo-embolic disease. He found that the incidence of metastases was much less in the treated group and survival was better: only one death though the expected rate was eight. These findings suggest that anticoagulant therapy may alter the natural history of cancer. Thornes (1967) found that the incidence of cancer in patients on anticoagulant therapy was one-sixth the expected rate in the general population.

Cliffon (1966) stated: "In the course of our experience with treatment of thrombosis in patients with cancer, we have had the impression that many of these patients improved not only so far as their thrombosis was concerned, but in their general well being."

He then treated a group of advanced cancer patients who had failed to respond to radiation or chemotherapy. Of 31 patients so treated, there was significant clinical improvement in 43%, no apparent improvement in 50%, and the results in three were inadequately recorded. Definite shrinkage of tumor occurred in 17%. This ranged from 35% shrinkage in one massive pelvic tumor and one upper abdominal carcinoma with liver extension, to complete disappearance of metastatic nodules in the groin and upper thigh in a patient with metastatic epidermoid carcinoma of the cervix. The longest survivor was 3½ years. This patient received one five-day course of daily infusions of fibrinolysin for metastatic reticulum cell sarcoma in the lungs. Cliffon noted that such advanced cases are an unfortunate choice. All therapists have found that such patients rarely if ever respond to any form of treatment.

The Fibrinolytic System and Cancer

The data reviewed here certainly indicate the need for much more serious clinical evaluation of anticoagulants given not merely alone but simultaneously with streptokinase and other agents which stimulate fibrinolysin in the patient. Such a regime should be combined with bacterial toxin therapy, BCG or Zymosan to stimulate the RES and aid in causing necrosis and absorption of the tumor or its metastases. The latter process may be facilitated by the administration of varidase to help absorb the necrotic tumor tissue with a minimum of toxemia or cachexia.

Ambrus (1960) believes the fibrinolysin system may play an important role in wound healing. He concluded that we have only scratched the surface of the biochemical complexity and therapeutic usefulness of this fascinating system.

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Interferon was discovered in 1957 by the late Dr. Alick Isaacs, of the National Institute for Medical Research, London, England. It is a protein produced by cells of different animal species, following incubation with inactivated or live viruses of many different kinds, which inhibits the intracellular growth of many different viruses in cells of the same animal species. (Isaacs and Lindemann, 1957). Interferon does not act directly on viruses but transmits a message to cells inducing them to form messenger RNA encoded for an antiviral protein.

This protein is slightly smaller than rabbit antibody globulin. Extracellular interferon stimulates intracellular antiviral activity that begins within one to four hours, increases rapidly and reaches a peak in from seven to twelve hours and may then remain constant for about 10 days.

Baron and Isaacs (1961) studied the presence of interferon in lung tissue of patients who died of influenza and found no significant amounts of interferon. They concluded that some patients may die of influenza because they cannot produce sufficient interferon.

They concluded that interferon is produced to protect the cell from any foreign nucleic acids. Only later in evolution did it become adapted to meet the invasion of viruses. They found that nucleic acid extracted from the cells of a normal mouse stimulate interferon production when introduced into chick cells, and vice versa, but that chick cells did not respond to their own nucleic acids.

Isaacs then found that when the fever is raised above the optimum for virus growth, a virus-infected cell produces interferon rather than more virus particles.

Because of the problem of species specificity, and other difficulties, some British workers fear that interferon may prove too expensive for general use, though it may find specialized uses, as in treatment of eye infections that would otherwise result in blindness. There is no obvious reason why injections of interferon should not be active throughout the body, but so far insufficient quantities have been available to produce more than a local effect.

Others in Britain are optimistic. One of the most promising possibilities is finding some way of inducing the cells of the body to make extra supplies of interferon

for themselves when viruses (including oncogenic viruses) attack. This might be done by inoculations either of attenuated viruses or with preparations of other nucleic acids or with bacterial toxins or BCG, and experiments along these lines are under way. Injections of various pyrogenic bacterial endotoxin preparations may prove to be the most practical for this purpose, since fever increases the synthesis of interferon.

Merigan, Petralli and Wilbur, at Stanford University, are working on interferon. Merigan reported in 1967 that interferon had been found active not only against a wide variety of viruses but other types of organisms as well. He reported that attenuated measles vaccine is a potent interferon stimulator. Children receiving primary measles immunization consistently demonstrated circulating interferon following attenuated vaccine administration. If smallpox vaccination is given 9-15 days after measles immunization the latter effectively blocks the vaccination; if concomitantly or 20 days apart, no effect: 83% takes in control children; 17% takes in the measles vaccine children. Interferon produced by measles vaccine is not active against all viruses.

Ho and Kono, working at the University of Pittsburg, found that an interferon-like inhibitor, can be induced by *Escherichia coli* endotoxin. They found that animals could be made resistant to the interferon-inducing effect of endotoxin by prior inoculation with the same endotoxin. Resistance appeared in 24 hours, persisted two or three days, was gone in six days. (Ho, 1964; Ho et al. 1965).

They postulated an inactivating factor in serum and indeed found that by incubating serum (collected 24 hours after endotoxin dose) with endotoxin they could abolish the inhibitor-inducing capacity of the endotoxin. The inactivating factor was also found to disappear when the tolerant state was over. Ho found the inactivating factor is independent of antibody rise and is probably not antibody.

Michaels, also at University of Pittsburgh, reported that the interferon-like viral inhibitor produced by bacterial infection resembled virus-induced interferon in several ways: it is active against the cell rather than directly against the virus; it is active against several different viruses and it exhibits cell-species specificity. It is sedimentably non-dialyzable, also like virus-induced interferon, but is largely inactivated by heat (56°C. for 30 minutes). Virus-induced interferon is more stable.

Borecky and Lackovic et al. in Czechoslovakia studied the effect of human erythrocytes and polysaccharides derived from *Candida albicans* (manna) and *Lysomyces starkei* (galactomanna). These all proved capable of interferon induction in vivo in mouse serum or in vitro in mouse peritoneal cells. The induction effect disappears from human erythrocytes stored for 48 to 72 hours.

Manna caused an early "endotoxic" type of interferon appearance and although induced interferon in the serum it did not do so in the spleen. Borecky observed that the finding that manna, with a relatively low molecular weight, functions as an efficient interferon producer is at variance with the hypothesis that the polyanionic character of a molecule should be responsible for interferon production.

There are several species of interferon according to Merigan of Stanford and Finter of Imperial Chemical Industries. Merigan reported a variety of non-viral agents induce interferon production: bacteria, rickettsiae, pleuropneumonia-like organisms, trachoma inclusion conjunctivitis agents, endotoxin, phytohemagglutinin, cyclohexamide and fungal products such as statolon, derived from *Penicillium stoloniferum*.

The largest interferon-inducing agent identified to date by Merigan's group has been toxoplasma.

The same virus has been found to induce different interferons, depending on which type of cell it infects.

In studies of statolon, Merigan found that it would induce a 90,000 molecular weight species of interferon in mouse serum and a 30,000 molecular weight species in mouse spleen, indistinguishable from viral-induced interferon.

Finter, one of Merigan's colleagues, found that a single injection of statolon (derived from *Penicillium stoloniferum*) protected pretreated mice for up to a month against a viral infection that readily killed two-thirds of the control mice. Finter also found that products of another mold have been shown to stimulate interferon formation. In 1966 he edited a monograph on interferons.

Some investigators think interferon could prove the most important medical discovery of the 20th century. If its early promise is upheld, it may cure every virus disease, including the common cold, hepatitis, influenza, pneumonia, polio, rabies,

yellow fever, chicken pox and measles. It also seems to be an effective agent against cancer.

In 1964 The Interferon Center, headed by Baron, Laboratory of Biology of Viruses, National Institute of Allergy and Infectious Disease, Bethesda, Maryland, was established under the auspices of the U.S. Department of Health, Education & Welfare. It gathers and disseminates data to interferonologists throughout the world. (Baron, 1966)

Cantell, Finnish State Serum Institute, Helsinki: Interferon is effective against most or all animal viruses, it spreads easily throughout the body, is a physiologic substance with little or no toxicity and is a weak antigen even in heterologous species. Limiting its present usefulness is the fact that it disappears quickly in vivo and thus provides short term protection.

Cantell said experience suggests two ways in which interferon may be used -- exogenous administration or stimulation of endogenous reproduction. Leucocytes now appear to be the best source for the substance. He described mass production of human interferon from human leukocyte cultures. This also has been done at the Institute for Cancer Research, Villejuif, France.

Cajal, at the Roumanian Institute for Inframicrobiology, Bucharest, reported that interferon had been prepared in mouse embryo cells with a virus recently isolated disease. It was administered to mice 24 hours before inoculation of the Hodgkin's virus and in a series of three post-infection doses at 24 hour intervals. This lowered the mortality by more than 40%, as compared to the rate in control animals. The survivors were found to be resistant to intra-nasal inoculation with lethal doses administered 30 days after first injection.

Allison, at the National Institute for Medical Research, London, reported that interferon has been produced in each of three tumor virus cell systems he has studied: the polyoma, Rous sarcoma and avian lymphomatosis virus systems. Tumor viruses cause relatively little cell destruction and tend to persist in infected tissues for long periods. Some tumor viruses interfere with the multiplication of other viruses, thus helping to "resolve" the initial infection.

In contrast, while not much interferon is produced by tumor cells, side infections with some tumor viruses can be used to prevent infection by other tumor viruses, thus

he has been able to prevent infection with chick tumor virus. However, others such as the ascites tumor cells are relatively insensitive to the action of interferon.

Friedman and Ralson (1964) reported that mouse cells infected with highly oncogenic strains of polyoma virus produced no detectable amounts of interferon, while less oncogenic strains of polyoma virus were good inducers. These findings suggest that the difference between variants in oncogenic potential may be due to the greater interferon production induced by the m variant than by the s variant.

Since the antiviral action of interferon is less marked in tumor cells than in normal cells, tumor cells often provide a favorable environment for persistent infection by interferon-sensitive viruses. However, because tumor cells can, with relative ease, become secondarily infected with viruses, it should not be concluded that viruses found in tumors had anything to do with their origin.

De Maeyer and De Mayer-Gurguard (1965) at the University of Louvain, Belgium reported that steroids seem to inhibit the production of interferon and so do carcinogens (methylcholanthrene and DMBA). They found the effect increased with increasing doses of carcinogen and they believe from their work that it is the synthesis and not the action of interferon which is thus blocked. Kilbourne et al. (1961) reported that cortisone inhibits the synthesis of interferon, thus enhancing virus multiplication.

Maria Luiza Duran Reynals, Albert Einstein College of Medicine, New York has shown that vaccinia virus can cause development of tumors faster when administered to animals with a carcinogen than when carcinogen alone is given.

Gressen et al. (1969) have studied interferon for about 10 years and reported that interferon treatment in the first three months of life significantly increases the survival time of male mice and diminishes the incidence of lymphoid leukemia. Where interferon treatment was continued for a year, survival time was increased in both male and female mice and the incidence of leukemia was reduced in both sexes.

Interferon is to some extent species specific. When prepared in chick tissues it is ineffective in calf cells, but when prepared in rhesus monkey tissues it is effective in man.

Several British pharmaceutical firms have been working cooperatively since 1961,

concentrating on producing pure interferon--a difficult task. Research workers in the United States believe it is a basic protein, the British workers believe it is acidic.

Soon after purification there is very little material left to work with: a liter of allantoic fluid from fertile eggs infected with virus yields only about one microgram of active material.

At first it was thought that interferon was not antigenic and therefore could not be neutralized by formation of antibodies. Evidence of an antibody against interferon was then discovered. (Paucker and Cantell, 1962).

Patients suffering from eye infections caused by vaccinia virus were treated by local applications of interferon and most symptoms cleared up in 24 hours. Trials on a larger scale have been carried out at the Common Cold Research Unit on volunteers infected with colds.

Hilleman, Director of Virus and Cell Biology at the Merck Institute for Therapeutic Research, West Point, Pa., has been working with interferon for several years, concentrating on finding ways to stimulate the body into making its own interferon. At present they are using double strand RNA extracts derived from *Penicillium funiculosum*. This is non-toxic and non-antigenic.

Kleinschmidt and Murphy (1965) working at the Lilly Research Laboratories studied the effectiveness of statolon, an anionic polysaccharide produced by *Penicillium stoloniferum*. A single injection of statolon protects mice against an m virus for two weeks.

Regelson, Professor and Chief, Division of Medical Oncology, Medical College of Virginia has been studying the effects of a synthetic pyran copolymer--which appears to act both as a direct antitumor agent and as a stimulant to natural host defenses mediated by the RES. (This polymer was developed initially as an industrial plastic of the type used as detergents, adhesives and structural components).

In animal studies on mouse leukemia (Friend virus) he found administration of this polymer prior to injection of the virus inhibited the leukemic process, provided the animals were pretreated four days to 24 hours prior to injection.

The mechanism of action of the compound was apparently to stimulate increased production of phagocytic cells by the RES, which in turn appeared to increase production of interferon.

Animal studies also demonstrated direct antitumor activity against a variety of solid tumors. On a cellular level the compound caused cell clumping, displacement of nucleic acid from cell nucleus to cytoplasm and other cell changes.

In preliminary tests on man, the compound was found to have similar effects: it induced the same type of cell changes, stimulated phagocytosis and increased interferon production.

Pyran is of particular interest because it induced interferon production in man to levels that are theoretically capable of clinically suppressing viral synthesis. The 38 volunteers to date were all advanced cancer patients.

Regelson is conducting these studies with Dr. Thomas C. Merigan, Jr., Chief of the Division of Infectious Diseases at Stanford University, School of Medicine, and Albert Munson, Springville Laboratories, Roswell Park Memorial Institute in Buffalo. (Personal communications.)

Stinebring and Youngner (1964) have studied the patterns of interferon appearance in mice injected with bacteria or bacterial endotoxin. They reported in 1965 that when mice are injected intravenously with bacteria or endotoxins, an inhibitor indistinguishable from virus induced interferon appears in the circulation. *Salmonella typhimurium*, *Serratia marcescens* and endotoxins from *Escherichia coli* produce peak levels of circulating interferon at about two hours after injection. Maximum interferon levels after injections of *Brucella abortus* or Newcastle disease virus are reached at 12 hours. Repeated exposure to endotoxin reduces responsiveness of animals to subsequent injections of toxins but prior injection with *Mycobacterium tuberculosis* (BCG) increases the reactivity of the host to endotoxin when measured by interferon response as well as by lethality. Infected mice showed a markedly enhanced ability to produce interferon following decreased doses of endotoxin: 3.2 micrograms produced the same interferon titre as 500 mg. in uninfected animals. They concluded that the same cells, probably phagocytic, are involved in the release of interferon following stimulation by

INTERFERON AND HOST RESISTANCE

endotoxin, BCG, Brucella abortus and Newcastle disease virus, despite the different time patterns.

Finding ways to combat virus infections or viral induced cancers has proved to be an extremely difficult medical problem. For about 100 years we have tried to prevent infections or infectious diseases by developing vaccines against them thus stimulating the host to produce specific antibodies against each disease.

With virus diseases there are so many different forms that it may be impractical, if not impossible to develop specific vaccines against them all. (Isaacs, 1961) Therefore means of stimulating non-specific resistance should receive greater attention, and interferon is one important factor in our resistance to viruses and apparently to cancer.

Where low grade virus or bacterial infections are widespread, the more pathogenic types such as poliomyelitis or oncogenic or leukemic viruses do not seem to get a foothold. Thus the incidence of paralytic polio and cancer is significantly lower in countries or peoples where the levels of public health and sanitation are not up to those in the relatively more prosperous countries.

Certain bacteria, endotoxins and polyanionic substances have recently been shown to induce interferon in vivo and in vitro. Interferon induction by non-viral agents in vivo involves different metabolic pathways suggesting that interferon may be present in a preformed state. Since it is now known that certain bacterial injections or their toxins and BCG can markedly increase the production of interferon, this effect may be one of the reasons why concurrent infections or bacterial toxin therapy have produced such remarkable results in various types of cancer. (224-227; 441; 486-491)

The fact that when fever is present cells produce more interferon suggests another reason why patients with acute febrile infections or in whom febrile reactions were elicited during toxin therapy appeared to have had more dramatic, rapid regressions and a higher percentage of permanent results than those with

mild or chronic infections that remained afebrile.

Wagner and Hwang (1965) in a review and analysis of recent observations on interferon noted that avirulent viruses are more effective inducers of interferon synthesis than the virulent viruses (748a). Recent reports by Riley (575, 570) on the beneficial effect of the LDH-elevating virus in leukemia therapy by asparaginase are of interest in their connection. Possibly part of this benefit may be due to interferon stimulation.

Interferon production is decreased by stress, steroids, antimetabolites, Actinomycin D and carcinogens.

Baron stated: "The interferon system could prevent viral oncogenesis in two ways: multiplication of the virus may be inhibited so that effectively there is less available for the transformation of cells to malignancy. The interferon system could also more directly inhibit transformation by preventing some essential intracellular event. There is evidence which indicates that both mechanisms may operate. ". . . Polyoma virus, Rous sarcoma virus and avian leukosis viruses can stimulate the production of interferon, and are susceptible to its induced antiviral action in cultured cells and intact tissues of several animal species. Under experimental conditions fewer tumors appeared when virus multiplication was inhibited by exogenous interferon applied in vivo, in ovo or in tissue culture. . . ."

Thus it would seem that interferon may be one of the most significant medical discoveries relating to man's resistance to a great many diseases, especially those of viral origin.

Activation of the host's inherent interferon producing system by administration of relatively innocuous inducing agents may be a feasible approach to the treatment of human viral infections and neoplastic diseases.

ATTEMPTS TO INCREASE HOST RESISTANCE IN CANCER PATIENTS

Few present day investigators are aware of the fact that surgeons of the 18th and 19th centuries (and before) empirically attempted to treat cancer by inducing reactions of the type we have been discussing by the use of counter irritants, vesicants, cautery, heat; also, due to unaided nature, countless acute infections occurred, principally pyogenic, thus providing a multitude of antigenic or non-specific stimuli. (Tanchou, 1844) That these could be effective in many cases is apparent from a study of a large series ~~of cases~~ such as those assembled by Tanchou (1844) or Nauts (1969).

Tanchou (1844) in a textbook on the medical treatment of cancer of the breast, with 300 observations, describes the methods in vogue in the 18th and early 19th century. Some quite dramatic regressions were recorded. We now realize that as a result of agents used to produce "counter-irritation", these empiric procedures were successful in stimulating the reticulo-endothelial and lymphatic tissues, ^{and} inducing delayed hypersensitivity reactions. These usually occurred as a result of vesicants and non-aseptic techniques which resulted in fever, local inflammation, erysipelas, suppuration or gangrene.

Wyeth (1894-1900) was one of the first to advocate inoculating streptococci into the wound following surgery for sarcoma, i.e. as an adjuvant to surgery in operable cases.

Matagne, of Brussels, Belgium, having observed a dramatic recovery of an inoperable cancer patient following an erysipelas infection, was probably the first to attempt to prevent recurrence of operable cancer following surgery, by administering injections of bacterial toxins (Coley toxins) before as well as after operation in order to increase host resistance. He reported his results in a series of papers (1899-1953), some of which are listed in our bibliography.

W.B. Coley (1891-1893) pioneered in this approach, but due to early adverse criticism to his method (injections of the mixed toxins of *Streptococcus pyogenes* and *Bacillus prodigiosus*, which is now known as *Serratia marcescens*), he limited his use of these toxins to inoperable cases from 1893 to/1903. Many of his

patients were very far advanced with extensive or metastatic tumors. Also the preparations available for use were extremely variable, and little was known of the optimum technique of administration, especially as regards site, dosage and duration of treatment. Since it is now recognised that advanced cancer patients are often anergic and immunologically unresponsive, it is not surprising that W.B. Coley and others treating such cases achieved few lasting favorable results.

By 1906 W.B. Coley was more aware of the importance of treating patients earlier in the course of the disease. He stated: "In every case there is a certain stage of equilibrium, a natural resistance power in some individuals which may prevent the disease from advancing, and if we can, by means of the toxins, do anything else to increase this resistance power and turn the scales, . . . we get success. . . . Many of the failures have been due to not giving enough of the toxins."

That year he initiated the use of his toxins as an adjuvant to surgery, in order to prevent recurrence or metastases. As mentioned above he was one of the first to advocate conservative surgery in certain types of sarcoma or giant cell tumor of the long bones in order to save the limb. This he felt was justified if one could give "prophylactic" toxin therapy to prevent spread of the disease following curettage or resection.

In 1933 he reported that the percentage of five-year survivals of patients receiving adjuvant toxin therapy for operable neoplasms was 50% higher than those treated by surgery alone.

Analysis of all the toxin treated cases in recent years indicates an even higher percentage ^{of permanent results was produced} if toxin therapy was begun before or immediately after surgery and given for a reasonable length of time (two to six months). Brief courses of less than a month were rarely effective. The end results obtained by toxin therapy alone or as an adjuvant to surgery and/or radiation are now being reported by Chambers et al., Fowler, Hager, Johnston, Nauts, Miller and Nicholson, Pelner (1953-1970).

Experimental work in recent years confirms the fact that various bacterial pro-

ducts such as BCG (Old, 1960, 1961) or yeast extracts (Diller, 1960, 1963) can increase host resistance.

Prigal (1961) reported the development of prolonged non-specific resistance to sarcoma 180 and staphylococcus infection following a repository injection of a lipopolysaccharide (*Escherichia coli*). No one, to our knowledge, has yet tried to use repository injections of bacterial toxins in cancer patients. This technique appears to deserve clinical trial.

Hattler and Amos (1966) reported that when mixtures of lymphocytes or lymphocytes and killed streptococci were injected into two advanced cancer patients the reaction was much more marked when lymphocyte and antigen were injected at the same site. They too commented that in advanced cancer, at least, there is a true depression of lymphocytic activity.

Stone, et al. (1951, 1955) attempted to induce resistance to recurrence or metastases in a small group of cancer patients by injections of sterile frozen autologous cancer tissue into the abdominal wall, in the hope that they would invoke a defensive reaction against the neoplasm. The only patient who remained well and free from further evidence of disease (a carcinoma of the sigmoid colon) developed multiple staphylococcal abscesses on the buttocks and back. The implants remained uninfected. The case is described in Fowler's monograph on cancer of the colon as case 19, series A (Fowler, 1969).

Christensen (1959) studied the growth of Brown Pearce carcinoma in rabbits treated with living or killed streptococci. He found that none of the rabbits receiving injections of living streptococci developed metastases, while metastases occurred in 50% of the untreated controls.

A group of Japanese investigators began working with streptococcal toxins about 1955 and they appear to have produced an effective preparation. In a review, Okamoto et al. (1965) summarized most of the data obtained in their laboratories with hemolytic streptococcal toxins in the treatment of experimental tumors. They achieved two distinct improvements in preparing their extracts: a) By suspending

the streptococci in Bernheimer's medium in contrast to simple media such as phosphate buffered saline, the tumor destructive properties of hemolytic streptococci were found resistant to heating at 45°C. for 30 minutes. This is of obvious importance since heat sterilization has been used in preparing these toxins for therapeutic use. b) Preincubation of live cocci suspended in Bernheimer's basal medium containing penicillin yields a potent anti-cancer preparation which is 20 times more effective than live cocci suspended without penicillin in inhibiting the growth of Ehrlich ascites carcinoma in mice.

Jordan et al. (1958) reported on the beneficial effects of Group A streptococci on transplantable leukemia in mice. Such treatment caused complete regression of the leukemia.

Hager et al. (1969-70) have recently studied over 70 different bacterial preparations, including the mixed bacterial toxins of *Streptococcus pyogenes* and *Serratia marcescens*, various strains of *Escherichia coli* as well as many commercial vaccines available for desensitization procedures. His preliminary studies were on Ehrlich ascites carcinoma, and showed that many of these preparations could increase survival or postpone tumor appearance time.

Nowotny et al. (1969-70) have detoxified the endotoxins of *Serratia marcescens* and they found that these purified fractions preserved their ability to stimulate host resistance.

Other investigators have noted that concurrent infections (both bacterial and occasionally viral) can favorably effect the resistance of mice or other laboratory animals used for assaying various anti-tumor agents. In some cases this is due to stimulation of the reticulo-endothelial system, in others possibly to stimulation or release of interferon, in still others to delayed clearing of Asparaginase as recently reported by Riley et al. (1968, 1970) which occurs with the LDH elevating virus in leukemia therapy with asparaginase.

Hirsch (1962) stated: "The non-specific stimulation of the host's immune responses to his own tumor by such agents as bacterial endotoxins, mycobacteria, per-

tussis vaccine, zymosan, etc. seems to be a promising approach."

The fact that bacterial toxins increase resistance not only to the cancer but to bacterial infections should encourage surgeons to initiate the injections shortly before surgery and to resume them immediately after operation, for such treatment will lessen the chance of infection, stimulate wound healing, and help destroy any cancer cells liberated during the surgical procedures.

R.T. Smith (1968) in a study of tumor specific immune mechanisms concluded: "The response to tumor antigens most closely resembles that involved in the rejection of normal tissue homografts in which relatively feeble histocompatibility differences exist. The tumor-specific immune response can serve to protect the host from progressive growth of tumor cells. . . . It appears now firmly established that immunologic mechanisms have a role in host resistance to tumors. In both the diagnosis and treatment of human cancer this element needs to be more freely explored and accounted. In certain cases in which it even now seems appropriate, the immune response should be permitted to gain fuller expression and to act synergistically with the established therapeutic tools. Moreover, certain avenues of prevention of a few human neoplasms seems near the horizon." He added that although the immunologic approach has not yet fulfilled the expectations of its most optimistic proponents, it requires consideration in the management of cancer patients.

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THE RESEARCH PROGRAM OF THE NEW YORK CANCER RESEARCH INSTITUTE

Believing that the immunological approach to the cancer problem offers the greatest hope for its solution, this Institute, since it was founded in 1953, has been analyzing various factors which may favorably or deleteriously affect natural resistance to cancer and allied diseases. When this resistance is depressed or inactivated by such factors as carcinogens, large doses of radiation, immunosuppressive drugs, cortisone, psychic stress, cigarettes or advanced age, cancer may develop and progress rapidly.

In the course of these studies a considerable number of cancer patients were found who had developed a complication which apparently favorably affected their resistance mechanisms so that their neoplasms decreased in size or disappeared. Since bacterial infections were associated with the largest number of such regressions of various types of cancer, special studies of these cases were undertaken.

Approximately 430 histories of cancer patients in whom an infection developed spontaneously or by inoculation have been abstracted in detail and analyzed. Of these 222 cases had microscopic confirmation of diagnosis and were followed at least five years after onset and 106 of the 222 were apparent successes, traced 5 to 54 years later. Of the 116 failures, 21 survived far longer than expected, i.e. from 5 to 30 years. (Nauts, 1969)

In addition, a total of 917 determinate cases of cancer treated by bacterial toxin therapy have been abstracted and analyzed. Of these 450 were followed from 5 to 72 years after onset of their neoplasm, but 86 of them died of their original cancers more than five years after onset, and 46 subsequently developed an entirely different type of neoplasm from 6 to 59 years after recovery from the first. Twenty-seven of these second primaries proved fatal. Four patients subsequently developed fatal acute myelogenous leukemia 23 to 57 years after onset of their original cancers. (Three had been given irradiation, two for their first, one for his second primary cancer.) At least 51 patients are known to have died of cardiovascular disease. Approximately 100 of these successfully treated cases are alive and well at the present time. (46 47 48)

In the majority of patients who developed concurrent infections or who received toxin therapy, the condition was inoperable when infection developed or toxins were begun. It is significant that 577 of these 1138 determinate cases (222 infection and 917 toxin treated) were traced 5 to 72 years after onset. The highest percentage of successes in the toxin treated cases occurred in the sarcomas of soft tissues or in the malignant lymphomas, especially reticulum cell sarcoma of bone. The slower growing more differentiated lesions were not as easily controlled, although remarkable results were obtained in treating 246 inoperable or metastatic carcinomas of the breast, colon, head and neck, uterus and ovary, lymphosarcoma, renal and testicular cancer, malignant melanoma and neuroblastoma and certain bone tumors, especially reticulum cell sarcoma of bone and giant cell tumors. In addition to complete or partial regression of such neoplasms, reduction or disappearance of lymphedema, ascites or pleural effusion were observed in certain cases following toxin therapy. Remarkable regeneration of bone destroyed by osteolytic bone tumors or bone metastases was also observed following toxin therapy.

sarcoma of soft tissues,

Excellent results were obtained in a high percentage of cases that were operable when toxins were begun, i.e., malignant melanoma, testicular and renal cancer, including Wilms' tumor, carcinomas of the breast, ovary, uterus and colon, malignant bone tumors and lymphosarcomas. In those patients toxins were usually given as an adjuvant to surgery and radiation. They appeared to be especially effective when begun prior to, during or immediately after operation or radiation.

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End result studies are now being completed on various types of cancer in which toxin therapy was used, including in such studies the recorded cases of concurrent infection, fever or inflammatory episodes, in order to determine more precisely the factors affecting success or failure in each type. (16-19, 33-4, 45)

Analysis of these data suggests that preliminary treatment with bacterial toxins (or an accidental infection) stimulates the natural resistance of patients so that they may tolerate subsequent surgery or radiation with a better response, i.e. more rapid wound healing, or more rapid destruction or absorption of tumor tissue with less deleterious effects on the general health. Recent work of Ainsworth in San Francisco, Hollcroft and Smith of the National Cancer Institute, and other confirms the fact that several types of bacterial toxins protect animals or patients against the lethal effects of subsequent radiation. The mixed toxins of *Streptococcus pyogenes* and *Serratia marcescens* were more effective in this respect than typhoid vaccine according to Ainsworth and Cole working independently. . . . Other studies published in Portland, Oregon indicate that mixed bacterial toxins given prior to irradiation in patients with tumors ordinarily resistant to the effects of radiation, may make it possible to achieve significant improvement in such cases. . . . Prigal has shown that a single emulsified injection of lipopolysaccharide during pregnancy protects the neonate against whole body irradiation (46). This should prove of significance in planning radiation treatment of pregnant patients.

Current research is directed at trying to improve the mixed bacterial toxins of Beta hemolytic streptococcus and *Serratia marcescens* (the combination originally known as Coley toxins) and at testing many other types of bacterial toxins, such as various strains of *Escherichia coli* or other microbial products to see if we may discover a preparation or a combination which may be more effective.

Extensive recent studies have shown that MBT administered to patients or animals, even in large doses, does not harm the normal tissues or organs. This is quite different from the immunosuppressive or other deleterious side effects which are observed with many of the chemotherapeutic drugs that are now being used in treating cancer, or when large doses of irradiation are given. (Fowler, 1968-70; Miller and Nicholson, 1971; Nauts, 1946-1970; Pelner, 1959)

Since the infections which seemed to be most effective in causing regressions of cancer were those which were accompanied by fever, an extensive study of the effects of heat and fever on cancer is being made, including analysis of end results according to the type of febrile reaction elicited in the toxin treated cases. It was found that three times as many inoperable patients were successfully treated if febrile reactions averaged 102°-104°F. than occurred in those in which little or no fever was elicited. (Nauts, 1946-1970) It is known that tumor cells are much more susceptible to heat than normal cells. (Crile, 1961-1963) Thus fever may be regarded as a desirable side effect. The febrile reactions last only a few hours.

It is now apparent that reticuloendothelial and lymphoid tissues play a significant role in natural resistance to cancer and these tissues are stimulated by certain bacterial infections or their toxins (when administered in suitable dosages). The site, frequency and duration of injections also appear to be important factors in successful therapy. Few physicians in the past were aware that some strains of streptococci and certain other bacteria or their toxins are able to stimulate a host response to substances or tissues which do not normally elicit such a response, provided they come into significant contact with the target tissue. This may explain why patients who received at least some of the injections locally did better than those who did not. Another reason may be local stimulation or release of interferon.

Since certain infections or microbial products appear to increase various immune responses, our investigators are studying how best to protect and activate the tissues responsible for such reactions and are evaluating how to use microbial products most effectively in various types of cancer and in different stages of the disease, alone or combined with other modalities and to determine more precisely how agents such as BCG or bacterial toxins exert their beneficial effects on cancer patients.

One of our investigators has clearly shown that living streptococci kill cancer cells in vitro within about 30 minutes without harming normal cells. A striking phase microscope moving picture film was made of this phenomenon. Bacterial toxins rarely affect cancer cells in vitro, but only in the living animal or patient. (Havas, 1963)

Interferon production is stimulated by viruses, bacteria and other micro-organisms, as well as by bacterial toxins and fungal extracts. This substance acts in one to four hours, much faster than other immune mechanisms. We may soon learn how best to stimulate this and other host resistance mechanisms in cancer patients by microbial or synthetic substances.

We must learn how to produce a lasting immunity. We believe that the discovery of non-toxic means of stimulating resistance can be a first step - and one that requires a great deal more intensive coordinated research.

DISCUSSION

or various microbial products

Since certain bacterial infections/appear to increase host resistance to cancer, it is important to evaluate how best to protect and activate the cells and tissues which take part in these immune responses so as to prevent cancer and treat it more effectively.

One must therefore avoid the indiscriminate use of immunosuppressive agents, including the corticosteroids, anticonvulsants and antibiotics. As regards the latter, Fowler (1969) stated: "Since there is now considerable evidence that acute concurrent infections, fever and inflammation may cause complete or partial regressions of cancer, or lessen the chances of recurrence or metastases following surgery, one must question the wisdom of giving antibiotics as a routine procedure before and after cancer operations. This point is of special importance in cancers of the gastrointestinal tract, as indicated by Zwaveling (1962), who found that preoperative disinfection of the intestines or colon is likely to promote the growth of spilled tumor cells. He concluded that tumor cells have less chance to grow in a milieu in which there was suppuration resulting from bacterial infection. He noted, moreover, that bacteria unaccompanied by suppuration did not inhibit tumor growth. He also warned that bowel disinfection (sulfasuxidine and streptomycin) favors the growth of recurrence or metastases. "Pathologists state that tumor cells will not grow in an intact bowel mucosa: infection of the bowel with organisms seems to be an important preventing factor. In modern times with routine bowel disinfection conditions may be altered, favoring the survival chance of the tumor cell." (1960)

"Cohn and Atik (1960, 1965) became interested in this problem and reported on the influence of antibiotics on the spread of tumors of the colon. . . . The possibility that control of bacterial flora might increase the rate of metastases from a tumor within the colon has not been widely considered in spite of Vink's paper in 1953, and the suggestions throughout the years, such as those inherent in the use of Coley's toxins, that there might be some connection between bacteria

and tumor growth." 7122 121

C.F. Miller and Ketcham (1962) observed a decrease in the implantation and growth of tumor cells in experimentally infected wounds in mice and reported that an intimate contact between bacteria and tumor cells was necessary for inhibition of tumor growth, since infection at a distant site had no effect on local tumor growth.

Of interest in this connection is the experience of Krishnamurthi (1961) in India who reported: "Where oral cancer coexisted with pulmonary tuberculosis the carcinomas were particularly radioresponsive. The oral cancers were proven histologically and the tuberculosis lesions both radiologically and by the presence of acid-fast bacilli in the sputum."

Others cited by Nauts (1969) have noted that patients having lobectomy or pneumonectomy for bronchiogenic cancer who developed pre- or postoperative infections such as empyema seemed to have a higher percentage of five-year survivals.

The critical importance of host defense mechanisms for successful treatment by surgery or chemotherapy has been demonstrated by Martin et al. (1961+1962) They used Sarcoma 180, Adenocarcinoma 755, and Walker carcinosarcoma 256 and studied the interrelationships of tumor size, immunotherapy and chemotherapy with surgery, Zymosan, cortisone, 6-mercaptopurine and Puromycin, etc. Their data show that "cure" can never, or rarely, be effected on large, well-established transplantable tumors by chemotherapy alone, immunotherapy (Zymosan) alone, or surgery alone. However, by combining these three modalities, they produced striking cure rates in the range of 70 to 80%, which could in turn be nullified by the simultaneous administration of an immunosuppressive agent such as cortisone. They concluded from these and other experiments on spontaneous tumors that there is a similarity between the therapeutic problem in cancer and that in bacterial infection; i.e., chemotherapeutic cure appears similarly dependent on the concomitant interplay of host defenses. A combined approach to the treatment of neoplastic disease appears indicated, in which stimulation of host defenses plays

a strategic role. Their data reveal a critical relationship between the dose of immunoadjuvant (zymosan) and the time of its administration. This factor, dose and timing, has also been clearly indicated in the use of bacterial toxins as a host stimulating agent as reported by Fowler (1958-1970), Nauts (1946-1971), Miller and Nicholson (1971) and Pelner (1959, 1960).

Diller (1960, 1963) and Mankowski (1957) made a thorough study of the beneficial effects of various yeast extracts. They found that a single dose of hydroglucan or glucan (purified forms of zymosan) can destroy almost 100% of transplanted tumors in animals. These agents appear to be more effective than bacterial toxins in certain animal tumors. They now appear to deserve serious clinical studies as immunoadjuvants.

Beginning about 1890 DeBacker (1897) used a preparation of pure yeast cultures, known as Backerine, successfully in the treatment of cancer patients. Manders (1897) stated that he had treated 60 cancer patients with this material resulting in 18 cures, some of several years' duration. Four of these had been operated upon, with rapid recurrence prior to initiating the inoculations. This treatment caused leukocytosis.

Old et al. (1960) have studied the beneficial effects of zymosan and BCG in stimulating the RES in tumor bearing animals. They found that zymosan protects against challenge with Sarcoma 180. Survival was increased twofold with BCG-infected hosts inoculated with Ehrlich ascites carcinoma. (493)

Biozzi, Halpern and their colleagues in Paris (1959-1963) have also studied the beneficial effects of BCG in stimulating resistance to various experimental tumors.

Weiss et al. (1961¹⁹⁶⁶) have reported on the protective effects of fractions of tubercle bacilli against isologous tumors in mice. At certain dose levels their non-living preparations were as effective as, or even more effective than, living BCG, but excessive quantities, even though considerably below the threshold of gross toxicity, sometimes accelerated tumor development. They con-

cluded that if progressive neoplastic disease is, in fact, a manifestation of immunologic deficiencies, it would be expected that substances which enhance both antibody production and the efficiency of the foreign body reactions will also increase resistance to the development of malignant tumors. It appears that this expectation has been realized in the tumor systems which were the subject of their investigations.

Mathé et al. (1968) in Paris have demonstrated the effectiveness of active immunotherapy in the treatment of acute lymphoblastic leukemia in children. They tried immunization by several means: a) non-specific by BCG; b) specific by vaccination with a pool of leukemic lymphoblasts, first formalized and then irradiated in vitro; c) combining active non-specific and specific immunotherapy in patients with acute lymphoblastic leukemia first treated with chemotherapy to induce a remission and given adjuvant chemotherapy following immunotherapy so as to reduce the number of leukemic cells to a minimum. Ten controls who did not receive immunotherapy after remission all relapsed. Of 20 patients given immunotherapy, 12 did not recur and 10 had lasted over 160 days after stopping the chemotherapy. The longest observed had survived 990 days when the report was published in 1968.

Alexander (1967) in London reported his experiences with immunotherapy at the Chester Beatty Research Institute in England, using a primary sarcoma of the rat. He noted a "relatively small increase in the host resistance may. . . be all that is needed to tilt the balance against the tumor"; and concluded: "Finally, it must be emphasized that at best immunotherapy can only be an adjuvant which eliminates residual disease after other forms of treatment - notably surgery - have removed the bulk of the malignant tissues."

Analysis of over a thousand cases of various forms of cancer receiving the first immunotherapy ever used at all extensively, namely bacterial toxin therapy (Coley toxins), indicates that the most effective combination therapy is to give such treatment prior to as well as after surgery, in order to insure absorption of some of the necrotic tumor cells as well as to reduce the size of the lesion

and the extent of the operation.

The percentage of recurrences or metastases was markedly lower in cases receiving such "prophylactic" toxin therapy, which was first suggested by W.B. Coley around 1905. In 1917 Coley stated that the indications for such treatment were: a) in practically all cases of inoperable sarcoma; b) before operation in sarcoma of the long bones; c) immediately after incomplete operations; d) in combination with surgery and x-ray therapy; e) after all operations for carcinoma or sarcoma to prevent recurrence. In 1933 Coley stated that if toxin therapy were given as an adjuvant to surgery for about six months he believed it more than doubled the five-year survival rates. This appears to be a conservative estimate judging by the end result studies recently completed or in preparation on those neoplasms in which a sufficient number of cases received adequate toxin therapy. (Nauta, 1946-1970; Fowler, 1953-1970; Miller & Nicholson, 1971) These data suggest that it may not be necessary to continue the injections for quite as long as six months to insure freedom from recurrence, but that injections should be started before or immediately after surgery or irradiation.

It is understandable that this form of immunotherapy and probably other agents such as zymosan or BCG can produce far higher percentages of permanent results, if it is begun before there is too great a mass of tumor tissue, after scar tissue or impaired vascular supply is present following surgery or radiation or before immunosuppressive cancer chemotherapy has been administered. This is especially important when treating older, more debilitated patients with slower growing, differentiated tumors since in these cases both the tumor and the patient may be less responsive to immunotherapy.

The only extensive series of patients other than cancer who are known to have received large doses of bacterial toxins (mixed respiratory vaccines) in order to increase their resistance to allergies, dermatosis, rheumatic diseases, etc. were treated by Baird, a Canadian allergist. (1968) He reported his experiences over a period of 50 years in a monograph at the conclusion of which he

discussed cancer and immunity. As regards his own work he stated: "It should be of interest to those doing research concerning cancer that of the hundreds of persons of all ages and both sexes who have had a course of bacterial antigen-antibody in large doses. . .none, to my knowledge, developed cancer afterwards. Whether this negative information is due to faulty observation or to some form of general resistance, I have no way of knowing. If the latter is the explanation it would be quite consistent with various recent ideas expressed by competent research workers. For example, suppose cancer represents some kind of reaction to viruses." He added: ". . .immunization with large doses of bacterial antigen-antibody seems to protect against known virus infections like the common cold, influenza, etc. Therefore, it would not be strange if sufficient resistance was developed to protect against the viruses causing malignant growths. Cancer . . .might be prevented from developing or even reversed by a sufficient antigenic stimulation with bacterial vaccine. In suggesting the development of a cancer vaccine, it has been suggested that it would be more potent as an antigen if accompanied by a bacterial vaccine as an adjuvant. Suppose some cancer cells are developing but the body is barely able to deal with them, might it not be that the stimulation of sufficient bacterial antigen would turn the battle in favor of the body? Let it be repeated that large doses of bacterial antigen-antibody might protect against the development of cancer or even reverse the cancerous process."

(32) He added that when investigators study this question it is hoped they do not use the trifling doses of bacterial vaccines which have hitherto been described in the majority of reports concerning therapy, but will employ doses many times as large.

Dosage is undoubtedly a critical factor in success or failure, however tumor bearing animals and patients tolerate much lower doses of bacterial products than those without tumors. This is especially true in the malignant lymphomas, including Hodgkin's disease and leukemia. If too large doses are used they may overload or block the RES, thus decreasing the resistance rather than enhancing it.

Weiss (1961) as noted above stated that excessive quantities of BCG sometimes accelerated tumor growth.

Ricks administered courses of influenza virus A and B and adenovirus #3 and 7 (0.5 cc) intradermally every month for two or three months for four years to a male patient who then developed adenocarcinoma of the colon. The lesion was resected in 1958. He was given two courses of x-ray therapy and one of nitrogen mustard. The disease progressed. Another exploratory laparotomy was performed. By 1961 the condition was terminal with massive ascites and pleural effusion due to widespread abdominal and hepatic metastases requiring daily paracenteses and thoracenteses for the ascites and pleural effusion. Prognosis was regarded as less than a week when Ricks started this man on a course of mixed bacterial toxins of *Streptococcus pyogenes* and *Serratia marcescens* (Coley toxins). Intradermal injections were given daily for 11 days. There was a very dramatic response: within three days there was no further ascites, followed by complete regression of the metastases and no further evidence of disease in the next 10 years, during which he remained in very good health. His only medication in this period consisted of injections of influenza virus A and B, and Asian strain, and adenovirus #3 and 7 (0.5 cc. each) intradermally, every month for two or three months spring and fall. These caused some local redness and skin reaction but no febrile reactions.

Possibly the very remarkable response to bacterial toxin therapy in this terminal case may have been partly due to the use of viral vaccines prior to onset of the carcinoma, and that subsequent courses of these vaccines spring and fall may have helped to maintain his immune responses, so that further metastases did not develop. These vaccines may also have stimulated interferon synthesis or release. This case is reported in detail by Fowler (1969) in his monograph on colon cancer.

In the past 15 years most of the experimental studies on transplanted tumors have been performed on inbred strains of mice in which extremely virulent tumors or leukemias have been used. These overwhelmed the animals already weak

resistance (due to inbreeding) and killed them in a matter of days. Inbred strains apparently are often less immunologically competent than the average human patient with or without cancer. Thus the experimental results in these assay systems of various microbial products which are known to produce stimulation of host resistance in operable or inoperable cancer patients (but rarely in the terminal stage) have not been given a chance to demonstrate their true possibilities. While increased survival time and postponement of tumor growth occurs there is not the dramatic very high percentages of complete regression and firm immunity against further transplants which were seen with Sarcoma 37 or Sarcoma 180 (Havas, 1958-1961; Diller, 1957-1963; and Johnston, 1962). At present there is a trend toward recognition of this problem and Old, at Sloan Kettering Institute, is among those who are including Sarcoma 180 and other more realistic tumor systems in their assays.

Such studies, together with the substantial volume of data assembled by the New York Cancer Research Institute in recent years, should furnish strong incentives for a reappraisal of present-day treatment of cancer. Immunosuppressive drugs should be used only as a last resort. Clinical trials ^{should now be made} of a variety of readily available host stimulating agents such as zymogen, a preparation of zymosan, BCG, many different bacterial toxins including those which show particular promise such as the mixed bacterial toxins of *Streptococcus pyogenes* and *Bacillus prodigiosus* (Coley toxins), Difco's *Escherichia coli* lipopolysaccharide strain #0127B8, Hollister Stier's *Salmonella paratyphi* or their mixed respiratory vaccine or that of Merck (Serobacterin) or Bogdanov's preparation of *Bacillus acidophilus* *Bulgaricus* known as AB.

It is quite possible that other combinations may prove even more effective.

Since tissue permeability may play a role in making cancers respond more rapidly and effectively to immunotherapy, further studies should be made on how best to utilize streptococcal enzymes such as hyaluronidase, streptodornase and streptokinase.

It would seem that dimethylsulphoxide should also be used in treating extensive inoperable cutaneous tumors or their metastases by surface application of immunoadjuvants. This combination might also be tried prior to surgery for accessible lesions involving the skin or subcutaneous tissues.

SUMMARY

In treating cancer patients now and in the future these data suggest that it may be extremely important to avoid anything which may weaken or destroy the reticuloendothelial or lymphoid tissues or suppress interferon synthesis or release. These include agents such as heavy radiation, immunosuppressive drugs (i.e. most of the cancer chemotherapeutic drugs), synthetic vitamin K analogues, antibiotics, antispasmodics or anti-inflammatory drugs, especially the corticosteroids. Although many of these agents have been observed to inhibit the growth of neoplasms temporarily, they tend in general to accelerate tumor proliferation and dissemination, and thus make permanent control of the disease impossible. Severe physical or psychic trauma, or major surgical procedures collectively classified as "stresses", also tend to decrease host resistance to cancer and allied diseases. Therefore immunotherapy should be used prior to surgery.

It is hoped that the data presented here, and by others working in this field, may now stimulate much more widespread clinical and fundamental research on how best to stimulate and protect the various host defenses so that the incidence of neoplastic diseases may be lowered both in man and poultry or cattle.

In addition, we must learn more about how to strengthen these defensive forces when cancer does develop, so that patients may combat the disease more effectively. These include the ability to evoke delayed hypersensitive reactions and other types of acute inflammatory reactions, interferon synthesis and release, leukocytosis and adequate antibody production, all of which seem to require an active lympho-reticuloendothelial system. Also of importance is better control of the fibrinolytic system in cancer patients by anticoagulants or by the use of bacterial toxins which seem to exert a similar effect in cancer patients.

In future we should attempt to use counter-irritants, vesicants and electro-cautery and injections of bacterial toxins or enzymes to evoke an acute inflammatory reaction in the region of the neoplasm while also invoking a systemic response by intradermal, subcutaneous or intravenous injections of bacterial toxins,

yeast extracts, BCG, synthetic polyanions or DNA digests in suitable dosages to mobilize the entire body's defenses effectively. Oral administration may also prove effective as indicated by the work of Bogdanov (493). Both specific and non-specific immune responses appear to be involved.

Duration of such treatment appears of great importance especially when dealing with inoperable cancer. As adjuvants to surgery or radiation the immunostimulating and anticoagulant agents can greatly lessen the percentage of recurrence or spread and enable the surgeon or the radiologist to use less mutilating operations and smaller doses of irradiation. This is of special significance in treating children.

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