

THE BENEFICIAL EFFECTS OF BACTERIAL INFECTIONS
ON HOST RESISTANCE TO CANCER
END RESULTS IN 449 CASES

*A Study and Abstracts of Reports in the World Medical Literature
(1775-1980) and Personal Communications*

Helen Coley Nauts

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CANCER RESEARCH INSTITUTE, INC.

1225 PARK AVENUE,

NEW YORK, N.Y. 10028

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INTRODUCTION

For over 200 years physicians have observed and recorded dramatic "spontaneous" regressions of various types of neoplastic disease. One of the first surgeons to consider the possible influence of host factors in the treatment of cancer was Pearce Gould who stated: "All therapeutic cures are obtainable only by the working of physiological forces and the first hope of therapeutic success comes with the observation of the efficiency of unaided nature to accomplish cure. . . . These cases, rare though they be, are the sum of our hope." (638)

In the last 20 years there has been an increasing interest in host resistance factors in cancer and for this reason so-called spontaneous regressions, whether complete and permanent or merely partial and temporary, have been studied intensively by a number of investigators, especially Everson and Cole (233-237) and members of the Cancer Research Institute (256-259; 284; 286-288a; 542a; 542b; 579-583k; 593; 642-656).

Certain factors seemed to be associated with the largest number of permanently successful results, namely concurrent acute bacterial infections, bacterial vaccines, or the removal of at least some of the tumor or its metastases (237; 256-259; 542b; 579-583k). Also of marked benefit in many cases were concurrent febrile or inflammatory episodes occurring without obvious infection. (582; 583i)

A large number of authors reported their individual observations of the beneficial effects of infections, bacterial vaccines, inflammation, fever or incomplete surgery (our bibliography contains over 1,000 references). However, until the present study apparently no one had attempted a) to determine which types of tumors were most frequently benefited; b) which types of infections or microbial products were most apt to be effective; c) whether other infections such as viral or protozoal infections might also be beneficial or whether they might actually have a deleterious effect on natural resistance to cancer; d) mechanisms of action. Such a fundamental study seemed essential to the ultimate development of microbial products which could be truly effective host-stimulating adjuvants in the treatment of cancer, or ultimately a possible means of preventing the disease.

It was found that in all types of neoplastic disease the majority of spontaneous regressions occurred following streptococcal infections (principally erysipelas), next in frequency being suppuration (staphylococcal or mixed infections). Many other types of bacterial infections were responsible for some dramatic regressions, as will be apparent from the present report. The largest number of permanent results occurred following the more prolonged staphylococcal infections.

The histories, 449 in all, have been grouped as follows:

Series A, 163 Cases: Pyogenic infections occurring spontaneously in inoperable cancer patients.

Series B, 58 Cases: Non-pyogenic infections occurring spontaneously in cancer patients (49 inoperable, 9 operable).

Series C, 117 Cases: Pyogenic infections occurring spontaneously before or after surgery

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in operable cancer patients (18 of these were apparently untreated, i.e., only biopsy was performed).

Series D, 5 Cases: Operable cancer patients in whom pyogenic infection was "encouraged" or actually induced.

Series E, 36 Cases: Inoperable cancer patients in whom pyogenic infections, mostly erysipelas, were actually induced.

Series F, 31 Cases: Inoperable cancer patients in whom attempts to inoculate or otherwise induce erysipelas failed.

Series G, 22 Cases: Mostly inoperable cancer patients in whom gangrene developed spontaneously or was induced.

Series H, 12 Cases: Mostly inoperable cancer patients in whom syphilis or malaria developed spontaneously or was induced.

Series I, 5 Cases: Inoperable Hodgkin's Disease.

Before presenting the actual case reports in these nine groups of cases, we will review some of the general observations made in the last 200 years concerning the effects of infections or infectious diseases on malignant tumors.

Tuberculosis and Cancer

Beginning with Rokitsansky in 1842 (720, 721) many authors reported an apparent antagonism between tuberculosis and cancer. (3, 19, 98, 107, 113, 114, 169, 176, 297A, 308, 315, 330, 333, 407, 437, 438, 460, 472, 479, 511, 577, 603, 623, 624, 640, 663, 685, 695, 699, 720, 721, 796, 854, 878, 931, 932) A few physicians discounted the possibility of any such antagonism. (92, 93, 239, 547, 709, 755, 932)

If one reviews the evidence carefully, it becomes evident that cancer and tuberculosis may occur in the same person, and if the tuberculosis is active and occurs concurrently, it may cause partial or complete regression of the cancer. For example, Bartley and Hultquist noted a slight tendency toward higher incidence of spontaneous regression in hypernephromas among patients with tuberculosis. (19) Haldane stated that "some pathologists, perhaps the majority, maintain that the two diseases are exclusive, that they depend on different and opposite constitutional conditions." (308) He considered as pertinent only cases in which both diseases were active. Williams stated: "It is obvious that there is a certain antagonism between active tuberculosis and cancer. The outbreak of cancer often follows or coincides with the healing of pulmonary tubercle, although in most cases the intervening period is fairly protracted." (932, p. 27)

A few authors such as Tromp cited evidence suggesting the possible counteracting influence of tuberculosis on the development or incidence of cancer in various countries or localities (878), i.e. patients who had had tuberculosis might be less apt to contract cancer.

Pearl concluded that cancer occurs less frequently in those with active tuberculosis than in the non-tuberculous. His study was based on extensive autopsy material at Johns Hopkins Hospital. Pearl suggested that cancer patients might be treated with tuberculin injections and this was done on a few patients at Johns Hopkins in 1929. (640)

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Among those who discounted the possibility of any such antagonism, Carlson and Bell stated that they had found no statistical evidence to support the view that cancer and tuberculosis are antagonistic. Their report was based on 11,195 postmortem examinations. However, they concluded that active tuberculosis was much less frequent among the cancerous than in non-cancerous subjects. (93a)

In the last 18 years a great many reports have discussed the beneficial effects of BCG on cancer. Old, et al found that certain strains of mice inoculated with Ehrlich ascites tumor when infected with BCG survive twice the expected time. (609) Biozzi, et al found that BCG administration produced increased resistance to tumor growth during the phase of reticuloendothelial stimulation. (45, 46)

That the mechanisms involved may be easily upset by the technique with which such injections are given is shown by the experiments of Viallier and Pellet who found that when a single injection of BCG is given within 24 hours of transplantation, there is reduced growth rate, but if repeated injections are given to rats with the Guérin tumor T⁸, the tumors grow at an increased rate. (897; 898)

Malaria and Cancer

A number of reports concerning the possible antagonism between malaria and cancer have appeared, especially between 1900 and 1910. (69, 182, 331, 463, 557, 618, 741, 742, 743) The first such case was reported by Trinka de Krzowitz in 1783: a patient with scirrhus carcinoma of the breast developed tertian malaria, followed by complete regression of the carcinoma in a few weeks. (877) Other cases in which complete regressions occurred were reported by Avromovici (15) Jovin (371) and Portanova. (677)

In 1931 Braunstein noted that in countries where malaria was prevalent there was 15 times less cancer than in those that were free from malaria, such as Denmark. He "attributed this to the fact that malaria increases the size and activity of the spleen, or more exactly the reticuloendothelial system." (69)

Again we find a number of authors who discounted any such antagonism. (158, 412, 501, 588, 688, 732, 782, 823) For example, Cook stated: "malaria is certainly no bar to the occurrence of carcinoma and I would earnestly protest against inoculating cases with the protozoan of tertian fever as a preventive of carcinoma." (158)

Kieffer concluded 1) There is no real antagonism between malaria and cancer. 2) Malaria infection supervening on the latter does not modify it. 3) Natives of tropical countries enjoy a relative immunity to malignant disease, which however, varies with wide limits. 4) The progress of civilization with the adoption of the ways of life of the white man materially diminishes this immunity." (379)

In the Dutch East Indies, Proschnik observed numerous persons suffering from concurrent cancer and malaria and never once saw the slightest amelioration of the cancer due to malaria. He believed that malaria was an indirect cause of a large percentage of liver cancer in that region. (683)

In a report on cancer in New Zealand, Hislop and Fenwick stated: "Malaria may not be antagonistic to cancer, but it is significant that where malaria is common, cancer

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appears to be rare. It may not be improbable that there is some malarial poison antagonistic to the growth of cancer cells. . . . New Zealand has the lowest cancer death rate in the world." (331)

Loeffler was the first to suggest inoculating malaria in cancer patients and reported unsatisfactory results obtained in two patients treated by Nocht about 1901. (463) Both these patients were profoundly prostrated by the malarial attacks. Thirty years later Braunstein attempted to activate the reticuloendothelial system of cancer patients with malarial injections, (69) He believed that the spleen was most involved in the body's defense against infection and assumed, *a priori*, that a patient's greatly enlarged spleen will produce specific and non-specific carcinolytic substances. He concluded that the entire reticuloendothelial system is activated through malaria inoculations in the same way as the spleen. He therefore inoculated tertian malaria into six patients with advanced recurrent inoperable cancer. He observed splenomegaly before the actual onset of malaria in most cases. In three of the patients with visible external growths there was hyperemia, swelling and pains in the tumor. In a case of carcinoma of the rectum and liver there was pain and tension in the tumor areas, and marked necrosis of tumor occurred with the onset of the fever. Temporary but marked regressions occurred. In conclusion Braunstein stated that malaria might be used to combat cancer, but only in the early stages and not in advanced or metastatic cases where the patient's reticuloendothelial system is no longer able to produce enough defensive material. (69)

Studies in Africa suggest that chronic malaria, which can be so debilitating, depresses the reticuloendothelial system, and may predispose children to Burkitt's lymphoma. (82a)

Although Wagner Jauregg inoculated malaria in the treatment of advanced syphilis (general paresis), (907) no further reports were found as to its use in cancer patients. However, since 1958 Corelli has been inoculating malaria in the treatment of thromboangiitis obliterans, with apparent success, i.e., healing of ulcerated gangrenous toes, and relief of pain and other symptoms. The first bacterial product ever used in Buerger's disease was Coley toxins, which produced complete and lasting cure in cases treated by Gray in a Veteran's Hospital over 30 years ago. (296)

Syphilis, Gonorrhea and Cancer

Amedée Latour in 1850 was the first to suggest inoculating syphilis in cancer patients. He stated: "All our alterants, most of our '*remèdes énergiques*', modify the entire organism, which it is of the greatest importance that we stimulate in order to cure diverse pathologic conditions." (428) If such a stimulus was not enough in treating incurable cancer he considered a more radical and profound disturbance, the inoculation of syphilis.

The controversy as to the possible antagonism between syphilis and cancer became quite heated at the meetings of the Royal Academy of Medicine in Brussels in 1851-52. (202) Ricord, a famous syphilologist, argued strongly against such an antagonism, and denied that prostitutes had a lower incidence of cancer than other women, due to their venereal infections. He attributed any lesser incidence to the fact that their trade was

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practiced at an age too young for cancer to develop, and if they develop cancer later they do not mention their earlier profession.

Didot wished to *prevent* cancer by what he called "syphilization" (induced syphilis). He believed such treatment could be prophylactic against cancer, not a curative measure. (201, 202) He stated that since ancient times it has been known that prostitutes never have uterine cancer, while the most common victims are good pious women given to celibacy. "In certain countries, such as Egypt, syphilis is endemic, almost everyone has it. One does not see cancer there, and if one does see a case, it is among transient strangers sojourning there briefly." (201) Baecker observed in 1897 that prostitutes who have gonorrhea seldom develop cancer. (17)

The few recorded cases of cancer patients in whom attempts were made to induce syphilis include that of Alquié in 1851, an inoperable recurrent carcinoma of the lower lip, on which he applied compresses soaked with pus from a very active chancre. There was marked improvement lasting a month. (10)

Didot inoculated pus from chancres on the back of the neck of a patient with mammary cancer. Symptoms of constitutional syphilis developed successively for a year, during which time the breast cancer diminished in size and the pain ceased. At this time mercurial treatment was instituted for the syphilis and the patient recovered. Auzias Turenne stated that in his experience several cancer patients seemed to be immune to syphilis. He emphasized that if one wished to induce syphilis in cancer patients one should not wait too long and one should not do so in terminal patients. In treating several inoperable cases he had observed no unfavorable complications, while a most notable amelioration occurred following the inoculations, which were continued until constitutional syphilis was produced. When the syphilis had become well established Didot destroyed it by what he called "syphilization" (repeated injections of small doses). He also believed that syphilis could be controlled by mercury, and concluded that "in any event these inoculations did not expose the patients to any danger." (201, 202)

These experiments were bitterly criticized by Ricord and others. (201) To our knowledge no one else ever attempted to induce syphilis in cancer patients. However, in 1883 Verneuil discussed the influence of spontaneously contracted syphilis on the course of the disease. He stated that the reciprocal influences of various diatheses were not yet well known, but the influence of syphilis on cancer seemed in certain cases to be quite definite. He cited several examples. (895)

In the first, a case of mammary cancer of one year's duration, the neoplasm progressed very slowly. Four months after onset the patient contracted syphilis, which appeared to hasten the progress and generalization of the cancer considerably. Verneuil added: "This unfavorable influence is apparently possible but nevertheless is not proven up to now, and cannot be, except by a large number of observations. One important point in this case was that, although far advanced, with multiple lymph node metastases (clavicular and axillary), *this patient did not suffer any pain*, although in this stage of the disease most cancer patients suffer a great deal. Verneuil added that he had observed many cases in which syphilis greatly ameliorated the pain of various neoplasms: "This is especially notable in cancer of the tongue, where pains are often excruciating." (895)

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At the Third International Cancer Congress in 1913 Wolff reported that Odier had observed that sarcoma patients attacked by syphilis did not develop metastases. (943, Vol. 3, p. 484)

Prior Health of Cancer Patients

A number of well known physicians in the past century have reported that cancer patients rarely had had infections or infectious diseases.

Laurence was the first. In 1854 he stated: "As a rule, it will be found that cancerous patients have otherwise been remarkably free from disease." He cited 21 cases in which he had noted the previous health, and in 16 of these it had been "unimpeachable", in the remaining five, illness had been of a very transitory nature. (430)

Lambotte stated that antecedent erysipelas and other suppurative diseases rarely occurred in the cancerous. He inferred that "*these maladies, by their vaccinal action protect against cancer.*" After analyzing 30 cases personally observed, he initiated a study by the Belgian Surgical Society which confirmed his own findings: antecedent pyogenic infections occurred in only five per cent of over 600 cases of cancer as compared with 80 per cent in the non-cancerous patients of the same age, sex and occupation. (422, 423)

Schmidt also noted this and stated: "He who escapes the Scylla of infectious diseases will most probably succumb to the Charybdis of carcinoma in later life." He found that of 241 cases of cancer of the chylipoetic system, 180 had never had any infectious diseases of childhood, and 99 went through life without any infectious disease of any kind. (766) He observed that when cancer patients are vaccinated against small pox a very weak reaction occurs and when they are exposed to poison ivy very little dermatitis is apparent.

The Decreased Incidence of Malignancy in Areas Where Infections or Infectious Diseases Are Endemic

Soegaard (813) and Kobayashi (327) observed that cancer is extremely rare in patients with leprosy.

Wolff noted that no cases of cancer were found in Germany among patients who had had typhoid fever. (943)

Voussoughitti noted that cancer and amebic dysentery are frequently seen in Iran, *but never in the same individual.* (905)

Ungar made a statistical study of all patients admitted to a hospital in Basle, Switzerland in a 20-year period 1927-1946. The prior incidence of acute infections and acute inflammatory episodes was almost nil in the cancer groups as compared with a much higher incidence in the non-cancerous group. (888)

In view of the above observations, one might expect that the incidence of cancer would increase in the civilized countries where preventative medicine, antibiotics and vaccines have cut down the incidence or severity of infections and infectious diseases so markedly.

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Jussawalla (Bombay) has reported that cancer is steadily assuming the proportion of a public health problem in India. This is mainly attributed to better control of malaria, tuberculosis and other infectious diseases. In Puerto Rico, life expectancy increased from 40 to 68 years between 1930 and 1958. In this period cancer rose from seventh to second place as a cause of death.

Levin (1912) appears to be the first to report on cancer incidence in American Indians, stating that it was extremely rare as compared with the white population in the same localities. He summarized the experience of physicians practicing up to 20 years with a population of 115,455 Indians and stated that only 29 cases of cancer were encountered in that interval. He added that cancer in whites in those states was just as frequently seen as elsewhere in the United States. He stated that it was not due to a lower proportion of Indians over 50 years of age, because the proportion was higher. He concluded: "The American Indians living under the same geographical conditions as their white neighbors may actually be nearly immune to the disease." (446)

R.L. Smith, et al. compared the present incidence of cancer and infectious diseases among the white and Indian populations of the United States and Canada. (803, 804) They found that the expected death rates for cancer were far lower in the Indians, while the rates for infective or parasitic diseases were over six times greater than the expected rate.

As regards the possible influence of endemic infections on the incidence or course of the disease in different populations, Burchenal, in a paper on "geographic chemotherapy" has recently studied the response of similar tumors from different geographic regions. It was found that Burkitt's lymphoma patients in Africa come from areas where malaria is hyperendemic, and most patients show evidence of previous malarial infection (enlarged spleen, malarial pigment, etc.) He postulated that this hypertrophy of the RES might also increase the capacity of the host to react to a specific stimulus. He then observed that the long term remissions seen in Burkitt's lymphoma in African children following chemotherapy are probably a result of a combination of chemotherapy and host defenses. (77)

M.G. Lewis, a pathologist who worked for many years in Kampala, Uganda, in a personal communication, mentioned the infrequency of metastases from malignant melanoma in Uganda, even when the primary growth was extensive. He noted that in most of these patients, the lesions were infected and ulcerated when first seen. The majority were on the lower extremities. (589)

These data furnish considerable evidence that where infections or infectious diseases are common, cancer is apt to be rare, or if neoplasms do develop, they may remain localized or they may respond more dramatically and permanently to chemotherapy or other forms of treatment.

Pyogenic Infections

Analysis of the various types of concurrent infections that were reported to have occurred spontaneously or by inoculation in cancer patients indicates that the largest number of dramatic and lasting regressions occurred following streptococcal (especially

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erysipelas), staphylococcal or other pyogenic infections. Undoubtedly in many of these cases, more than one organism was involved, and these may have acted synergistically.

While most of the present day surgeons have ignored the possible benefit that may occur if infection develops in a case of malignant disease, a number of prominent physicians and surgeons in the 18th, 19th and early 20th centuries were well aware of this phenomenon. (851) They reported that patients who developed infections or inflammatory episodes before or after surgery for cancer had a significantly lower incidence of recurrence or metastases. Among these were two in 1909, Odier (601) and Thiery (859) and one in 1927, Michaeloff. (540) A few others are cited below.

In 1901 Rodman, in discussing hip joint amputation for sarcoma, stated that he believed "infection should be invited" as a means of preventing recurrence. (949) W. B. Coley remarked à propos the question as to whether the early results of operations for sarcoma were better than later ones, and the statement that if the theory of infection held true, they ought to have been better, that a careful reading of Gross' classical article on bone sarcoma would convince anyone that those early results *were* better. Gross' paper indicates that postoperative infections occurred in those pre-antiseptic days, and that better immediate and final results *were* obtained. (303) Coley concluded that there was no more logical way of explaining these better results except on the theory of infection.

Because of such observations, Wyeth, whose paper was being discussed, had also concluded that surgeons should encourage or induce infection in their cancer patients. He stated: "In regard to the question of advisability of an immediate infection of the stump after an amputation, or a secondary infection induced after all the acute inflammatory symptoms caused by the operation have subsided, it would be determined somewhat by the condition of the patient at the close of the operation. In an anemic subject with low resistance, it would probably be more dangerous and increase the mortality of the operation to infect the stump at the time of operation. However, when the patient is in good condition, I would prefer to infect the stump at once. Fortunately, the majority of cases are in excellent condition following the operation." (949) In these he insisted upon immediate infection for the following reasons: "First, it does not materially add to the danger of death from the operation; in the second place, these patients when they have recovered from the immediate effects of the amputation, feel so well that it is difficult to get them to return for an infection, and the tendency to recurrence is so great that it is safest for them to run the small additional risk of a streptococcus infection rather than the return of the disease even though it may seem dangerous and may be construed by some to be unsurgical . . . (949)

In reporting a case of osteosarcoma of the femur who remained entirely well six years following post-amputation pyemia with multiple abscesses, Coley further stated: "The cure of sarcoma of the femur by high amputation is so rare that every success should be reported. . . . The results of operation for sarcoma of the femur and of the long bones in general in pre-antiseptic days . . . were much superior to those obtained today. The explanation that I have offered, and the only one that seems plausible, is that the streptococcus infection that not infrequently occurred in the earlier period destroyed the sarcoma cells that were left behind and prevented recurrence." (135, p. 87)

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In 1950 B. L. Coley discussed end results in his series of 12 cases of osteogenic sarcoma following hemipelvectomy: All of the cases in this group have done very badly and have promptly metastasized after an interval which does not seem to us to have justified the procedure had we known how brief it would be. This is in contrast to chondromyxosarcoma where most of them had had at least a good year of palliation and several are living at intervals of 1½ to 4 years without evidence of disease." (Letter to physician who referred such a case). (528) Recent analysis indicates *that most of the cases B. L. Coley referred to who survived had developed some form of postoperative infection.* (589)

DaCosta, in his textbook on surgery stated: "Occasionally suppuration cures a sarcoma. A study of statistics seems to indicate that more cases of sarcoma are cured after operation if the wound suppurates than if it remains aseptic, and it has been proposed to infect the wound deliberately with pus germs to lessen the danger of recurrence. . . . It may be infected at the time of operation or soon after." (177)

Grey Turner of England stated: "It is significant that those cases of carcinoma of the colon in which the growth was complicated by abscess formation often did extremely well. (300, p. 962) Dunphy made similar observations in 1947. (215)

More recently Liechty et al. noted that patients with cancer of the colon or rectum who develop intraperitoneal infections and survive them have an increased five-year survival. (453a)

Meyer and Benjafeld (1955) asked if it is not possible that a contributory factor to the increase in cancer may be the destruction of certain bacteria by antibiotics, thus absolving the body from bringing the normal immunological mechanism into use, a mechanism that has been acquired and perfected through millions of years. (538)

A few thoracic surgeons have become aware of the salutary effect of severe postoperative empyema on survival of lung cancer patients. Sensenig et al. were the first in 1963 to report on this observation. They stated: "An analysis of the few patients who developed postoperative empyema revealed that three of the seven survived five or more years, and four of the seven are still alive without known disease." They added: "In view of the experimental evidence that both gram positive and gram negative bacteria produce antitumor substances, the subject bears additional investigation." (781a)

Le Roux, in Edinburgh, reported in 1965 on a clinical study of survival of patients with lung cancer and severe postoperative empyema. In this series of 3565 cases of lung cancer, 49 patients developed empyema. He noted that in the empyema patients survival was surprisingly good. (442a)

Blake and Clifton, in 1967, reporting on their experience at Memorial Hospital, noted that analysis of postoperative empyemas revealed that patients who survived five years tended to have had more streptococcal and staphylococcal infections, and infections with larger number of organisms. They added: "Certainly with clearcut laboratory evidence of potent oncolytic activity by virus and bacterial products, clinical application needs to be continually reassessed. (49a)

Sensenig et al. (1963) noted the salutary effects of severe postoperative empyema on the survival of lung cancer patients. (781a) Takita (1970) noted that 54 per cent of his lung cancer patients who developed postoperative infections survived five years. Sta-

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phyllococcus and *Pseudomonas pyocyanea* were the two organisms most frequently isolated. (850a) Ruckdeschel, et al. (1972) reported 50 per cent of his 18 lung cancer cases with empyema survived, as compared to 18 per cent of the non-infected group. (752a) Greentree (1973) reported a fifteen year survival in a case of anaplastic lung cancer with lymph node metastases who developed severe pleural infection after receiving an injection of olive oil into the pleural cavity. (297a) These observations led McKneally and others to use BCG intrapleurally in their lung cancer patients (485a). We believe better results would occur if bacterial vaccines were used on these patients before and after surgery.

In 1844, Tanchou, a well-known physician in Paris, reported on over 300 cases of breast cancer treated medically. In most of these cases "laudable pus" developed. Physicians of that period encouraged this by counter irritants and other local applications. (851)

One may ask why such observations were not more widely known or did not occur more often in the experience of oncologists during the past 80 years. Even in the early days, prior to vaccines and antibiotics, Williams noted in 1897: "The comparative rarity and slight intensity of febrile complications of cancer is a noteworthy feature of this disease." (930)

W. B. Coley, Wyeth and others who attempted to inoculate erysipelas in their cancer patients found that in about half the cases they could not produce an infection. This may have been due in part to the use of attenuated cultures, but also to the fact that cancer patients may not be able to respond to such inoculations by the acute inflammatory reaction and fever characteristic of erysipelas.

In 1920 Laumonier discussed the work of the German or Austrian physicians such as Wagner Jauregg who were then using fever therapy by inoculating malaria. He stated: "The fundamental idea of these therapeuticists was that clinicians had already observed for a certain time that a concurrent febrile affection could modify the course of a chronic condition, slowing its progress, or even causing a remission. Thus, typhoid may markedly ameliorate general paresis; small pox, prolonged whooping cough, erysipelas, cancer." (429) The acute infection was believed to act like a whiplash on the natural defenses and to stimulate reactions which are often quite intense, the leukocytosis being especially important.

In this connection, it is of interest to consider that from about 1945 abdominal surgeons used antibiotics routinely in order to sterilize the bowel preoperatively. Until about 1960 no one apparently considered the possibility that such a procedure might actually increase the incidence of recurrence or metastases in the colon or the tissues traumatized at surgery. The work of Cohn and his associates (119, 120, 919) and Zwaveling (960) and more recently Herter and Slanetz (325) have clearly shown that this technic is unwise. Cohn reported that *the control of the bacterial flora of the colon significantly increased the incidence of tumor growth in the anastomosis*. (119) Zwaveling reported that *tumor cells have less chance of growth in a milieu in which there is suppuration resulting from bacterial infection*. He added that "the current surgical methods (preoperative surgical disinfection) reduce the chance of tissue degeneration

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and therefore increase the possibility of growth of tumor cells that have spilled in the wound." (960)

Weilbaecher, et al. further reported that "bacteria exert an inhibitory effect on tumors of the colon." (919) They cited Miller and Ketchum (542) as showing a decrease in the implantation and growth of tumor cells in experimentally infected wounds in mice and reported that *an intimate contact between the bacteria and the tumor cells was necessary for inhibition of tumor growth.*

For surgeons who now hesitate to abandon the use of antibiotic bowel preparation prior to colon resection, the retrospective study of Herter and Slanetz of 1042 colon resections at Presbyterian and Frances Delafield Hospitals, is of interest. (325) They reported that general postoperative complications occurred with parallel frequency in the patients who received preoperative intestinal antibiotics and those who were prepared by mechanical measures alone. "Staphylococcal enteritis developed rarely, *but with greater frequency following antibiotic preparation.*" They also mentioned the problem of super-infection in the form of unopposed fungal or pathogenic bacterial growth following sterilization. (325) The discussion following this interesting paper indicates that an increasing number of experienced surgeons are now avoiding the use of antibiotics with excellent results.

However, these highly trained men, working with cancer of the colon are among the few modern surgeons or physicians who have recognized the possible importance of bacteria or their vaccines in host resistance to cancer. Several thoracic surgeons (as noted above) have reported that patients with bronchogenic carcinoma who develop empyema following pneumonectomy fare much better as regards survival than those who do not become infected. (485a, 781a, 849a) Other physicians such as Meyer and Benjafield (467a) have called attention to the fact that the incidence of lung cancer had increased dramatically precisely in the period when various modern procedures including antibiotics have prevented or controlled respiratory infections including tuberculosis. They stated:

"If . . . cancer is due to a virus, may we not conclude that by damaging the tissues in some subtle manner the antibiotics may absolve the body of the need to bring the normal immunological mechanism into use—a mechanism that has been acquired and perfected through millions of years of evolution and which seldom fails, and furthermore may upset the bacteria-virus balance and so predispose the tissues to invasion by cancer cells?" (467a)

In 1975 Clarkson et al at Memorial Hospital in New York analyzed the histories of their acute myelogenous leukemia patients to see why some of these adults had much longer remissions. (112a) They found that most of the long-term survivors had received *Pseudomonas aeruginosa* vaccine in order to prevent fatal septicemias so prevalent in these cases. As a result of this finding, acute myelogenous leukemia patients now receive *Pseudomonas aeruginosa* vaccine as a part of their therapy.

Precisely because of the development of aseptic surgery, vaccines and antibiotics, physicians since 1900 have had few opportunities to observe the possible benefits of untreated concurrent acute infections in their cancer patients.

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If, in analyzing the available material on this subject, we eliminate from consideration the well documented cases published prior to 1900, as was done by the only comprehensive study of spontaneous regressions of cancer ever to have been published, (237) we are deprived of a great deal of significant data which may help us to learn more about the fundamental physiological mechanisms involved in these remarkable responses of apparently hopeless cancer patients to various types of concurrent infections, fever or inflammation. Careful study of these detailed histories is yielding greater knowledge of the mechanisms of action, so that present and future experimental and clinical research may be planned more intelligently in order to develop various microbial products as effective host stimulating adjuvants to surgery, radiation or chemotherapy, or as primary treatment in cases not amenable to conventional modalities for whatever reasons.

The recent studies of Martin, et al (508, 509) indicate the importance of combining a host stimulating agent with partial surgical removal. They used a yeast extract, zymosan. Alteration of host defense mechanisms by large amounts of tumor tissues appears to be responsible for the failure of otherwise curative courses of chemotherapy to eradicate well-established cancer. Reduction of tumor size by simple surgery restored the curative efficacy of chemotherapy. Their data showed that "cure" can never or only rarely be effected on large well established tumors by chemotherapy alone, immunotherapy alone (zymosan), or surgery alone. However, combining the three therapeutic modalities produced striking cure rates in the neighborhood of 70 to 80 per cent, which could in turn be nullified by the simultaneous administration of an immunosuppressive agent (cortisone). The findings suggested that there is a similarity between the therapeutic problem in cancer and in bacterial infections, i.e., chemotherapeutic cure of cancer appears similarly dependent on the concomitant interplay of host defenses. Martin suggested that a combined immunologic and chemotherapeutic approach to the treatment of neoplastic disease appears indicated. (507, 508)

Havas, et al, also observed the beneficial effect of tumor removal on the end results of treating mice with bacterial vaccines. (319) Apparently many of the failures among the infection cases included in the present study died as a result of the deleterious effects of absorbing huge quantities of necrotic tumor tissue which had been too rapidly destroyed during the infection. If in these cases more surgeons had attempted to remove some of the growth or to evacuate the necrotic tissue, the results might have been different.

Thus, the present study indicates the wisdom of Martin's and Havas' observations. Most of the failures had a) advanced or terminal cancers; b) the general condition was markedly affected by the disease or prior treatment when infection developed; or c) the patients were elderly, with depleted immunological responses.

Beneficial Effects of Bacterial Infections on Radiation Therapy

Patients in whom bacterial infections or fever developed prior to or during radiation therapy may respond very dramatically to even minimal radiation therapy. For a clearcut example, see Series B, Case 58, page 91. This 37 year old male had a very

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extensive inoperable bronchogenic carcinoma with widespread pleural metastases. He had pneumonia, pleurisy and leukocytosis (23,600) prior to exploratory surgery, followed by fever to 103°F. Cases in which this occurred following bacterial vaccine therapy are found in the end result studies of Fowler (256-260); Miller and Nicholson (542b), and Nauts (580-583j).

That this *increased radiosensitivity* of the tumor really occurs without rendering the skin or other normal tissues more vulnerable to the radiation is of great significance (210, 311). These findings suggest that in treating patients now and in the future one may use lower doses of irradiation if the immunopotentiating and radioprotective bacterial vaccine injections are begun prior to radiation and continued during and after such therapy. This is of special importance in treating children in order to avoid the deleterious effects on skeletal growth or kidney function, as well as avoiding the possible leukemogenic or sarcogenic effects of larger doses of radiation, (583a)

The markedly beneficial effects of certain bacterial infections or bacterial vaccines in *protecting patients against the deleterious effects of radiation on normal tissues* is receiving increasing attention. In order to exert their greatest benefit, the infection must occur or the vaccines must be administered *prior* to the irradiation. (4-6, 102, 121, 210, 335, 806, 807) A number of cases in the present study suggest the marked protection afforded by prior infection, thus enabling the patient to tolerate subsequent radiation with less deleterious effects, while potentiating the response of the tumor to the radiation.

Mechanisms of Action Involved in the Markedly Beneficial Effects of Bacterial Infections or Vaccines on Cancer Patients:

It is now known that certain strains of streptococci, staphylococci and certain other strains of bacteria are able to stimulate a host response to substances or tissues which do not normally elicit such a response in an animal or patient. For example, Glynn and Holborrow found that four strains of streptococci and a strain of *Staphylococcus aureus*, when grown on agar media, gave rise to agar antibodies in antisera prepared against them. (285) Burky found that by combining staphylococcus with lens substance, rabbits were sensitized to lens and developed high precipitin titres to lens tissue. (83)

In order to stimulate this response, the organisms do not need to be alive, but the bacteria or their vaccines must come into significant contact with the target tissue. These findings suggest why more dramatic and lasting results were observed in cancer patients who developed infection *in or near the tumor area*, or who were given at least some local injections when receiving vaccine therapy.

The *role of fever* in the apparently beneficial effects of infections or of bacterial vaccine therapy in cancer patients must also be considered, for tumor cells are much more thermolabile than normal cells. (651, 652) Crile has shown that heat and radiation are synergistic or at least additive in their effects on tumors when given within a few hours of each other. (167) Analysis of end results in patients receiving bacterial vaccine therapy as regards the febrile reactions elicited, indicates that the percentage of perma-

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nent results were significantly higher in patients with reactions averaging 102°-104°F., and that this was especially evident in the inoperable cases. (307, 583i)

The role of streptococcal enzymes or other bacterial enzymes must also be considered in the response of cancer patients to concurrent infections. These include hyaluronidase, streptodornase and streptokinase: a spreading factor, a fibrinolytic factor and a mucinolytic factor. Each may play a helpful role. The first by enhancing the permeability of the tissues so that the cellular and humoral immunological defenses may be more rapidly mobilized and transported to the tumor cells. The second lessens the chance of tumor thrombi forming and thus lessens the chance of metastatic spread. The third may render the tumor cells more vulnerable to the bacteria or their vaccines.

Extensive studies on *the role of fibrinolysin* in reducing the incidence of metastases have been performed by Clifton, Grossi, Agostino, the Fishers, Omeara and Thornes. The subject is discussed at some length in two chapters of a monograph edited by Wissler, Dao and Wood (940). 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 coagulative factor in cancer cells can be blocked in the human and the rabbit by dicumoral type anticoagulants. (866, 940).

Clifton and Grossi found that administration of human fibrinolysin to rabbits diminishes the mortality and is highly effective in preventing metastases by inoculation of V2 carcinoma or Brown-Pearce carcinoma cells in rabbits. (115)

These findings help to explain why streptococcal infections were responsible for so many of the so called spontaneous regressions which occurred following concurrent infections in cancer patients.

One of the first to emphasize *the role of the lymphocyte* in resistance to cancer was Murphy, at Rockefeller Institute. (570) More recent research confirms the fact that the availability and integrity of lymphoid tissues appears to be important for adequate resistance to cancer and allied diseases.

At least two studies have been made of the relative incidence of cancer or leukemia in patients who have had appendectomies or tonsillectomies. McVay analyzed 914 cases coming to autopsy in three institutions and concluded that cancer of the colon and to a lesser degree, the lung, breast, cervix, stomach and pancreas, may be organs on which the appendix may confer some protection. (487)

Independently Bierman has confirmed these findings in a study of 1,287 consecutive postmortem records and in 122 living patients with lymphomas and leukemias. These data suggest that a systemic and local protective effect is produced by the appendix. (43)

Recently a number of surgeons have raised the question of whether radical lymph node dissections are truly of value or whether these procedures and radiation of lymph nodes may lower the resistance of the tissues to metastatic spread and thus decrease the likelihood of a permanent result. For example, Block and Hartwell stated: "We found no evidence in our experience that . . . a prophylactic node dissection is better or worse than local excision alone. . . . and we disagree with the dogma of Pack that the elective or prophylactic lymphadenectomy must be done routinely to adequately treat malignant melanoma." (52) They cited several other surgeons who had reached

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the same conclusions, including Lund and Ihren, who believe therapeutic lymph node dissection is of value only in a small number of cases.

Crile, in a recent monograph describing his simplified treatment of breast cancer, emphasized that it is time we take steps to eliminate the needless morbidity associated with radical treatment of breast cancer. "Regional lymph nodes are important to immunologic resistance and this immunity may be destroyed by either removal or irradiation." (168) Strauli stated that Engeset found the barrier function of lymph nodes in rats is destroyed by local radiation. (839)

Bacterial infections or their toxins stimulate the functional capacity of lymphoid tissues so that they may be mobilized more effectively in cancer patients. Hyperplasia of lymph nodes, leukocytosis, more rapid healing of wounds or ulcerated areas and regeneration of bone destroyed by the neoplasm have all been observed during or following acute bacterial infections or bacterial toxin therapy. (256-259, 579-584, 651)

The role of iron has been recognized as an important regulatory factor in the balance of host-parasite interactions (919) and some strains of virulent bacteria are known to acquire the capacity to sequester iron from their environment both *in vitro* and *in vivo*. (301) It has also been suggested that one of the mechanisms of the beneficial effect of fever on the course of infection relates to the accompanying hyposideremia and consequent reduction of the availability of iron for bacterial cell growth. (227) The possibility that iron, bacterial infection, fever and tumor regression are connected has not been explored. It is of interest to note, however, that recent studies of the nutrient requirements of transformed cells *in vitro* and growing tumors *in vivo* have shown that both *in vitro* and *in vivo* tumor cells utilize iron in a fashion possibly similar to bacteria (247a) and also through the expression of surface receptors for the iron binding protein transferrin. (309a)

The effective competition of bacteria for a nutrient indispensable for tumor cell growth, could play an important role in the reported regressions of cancer associated with severe bacterial infections. In addition, recent work on the action of iron on a number of immunological functions tested *in vitro* (74a, 196a, 593, 593a) and on the immunological function of patients with iron overload (372) has indicated that both iron and ferritin have immunosuppressive effects on macrophage (919a) and T-lymphocyte function. (521)

These observations have led to the postulate represented diagrammatically in Figs. 1-3. (de Sousa, personal communication) According to this postulate, a fine balance seems to have evolved between bacterial infection, iron deficiency, fever, immune function and tumor cell growth. (Fig. 1)

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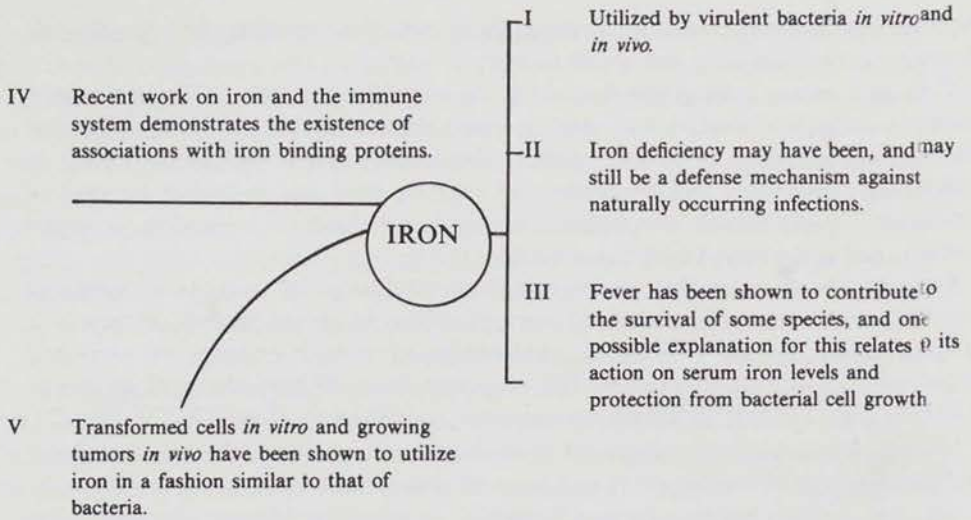
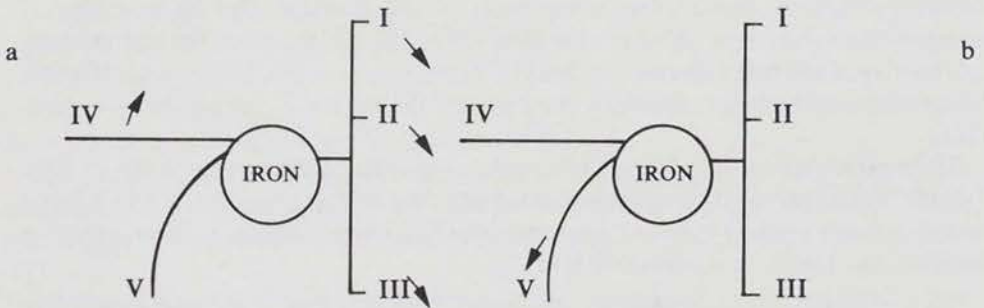


Fig. 1 Summary of interactions possibly mediated by the presence of iron in the development of certain forms of infection and cancer, and abnormalities of function within the lymphoid system.

If weights are placed in either I: II: III: or IV (Fig. 2a), the chances of V (tumor cell growth) prevailing are minimized.



Figs. 2a and 2b.
Balance indicated by arrows
against (2a) or in favor (2b)
of tumor cell growth.

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If, on the other hand (a) the incidence of infection is reduced, (b) the frequency of iron deficiency is decreased by the use of iron supplemented and iron rich diets, and (c) the immune system is partially suppressed by exposure to iron (as part of the physiological cycle) and other metals (as part of increased occupational and environmental exposure to metal pollution), the prevalence of V becomes unavoidable. (Fig. 2b)

One possible value of this model is that it could help to clarify some of the mechanisms underlying the effective action of bacterial toxins in the cases reported by Coley and others, and the cases of spontaneous remissions associated with severe bacterial infections collected in this monograph.

Evidence for and against this concept is presently being reviewed by Weinberg. For example, it has been found that some rat and human mammary cancers contain three to ten times the amount of non-heme iron present in normal mammary tissue. (918c)

The *role of the reticuloendothelial system* in host resistance to cancer and the effect of concurrent bacterial infections or vaccines on its functional capacity: For over 40 years a considerable number of investigators such as Zacherl (953), Stern (827-829), Perner (647) and Old, *et al* (610, 611) have reported on the apparently significant role played by the RES in resistance to cancer. It is now clearly evident that all the reticuloendothelial and hematopoietic tissues are markedly stimulated during or following certain bacterial infections or the administration of suitable dosages of various microbial products such as the Coley vaccine, and those of staphylococci, *Pseudomonas aeruginosa*, *Escherichia coli*, pertussis and *Brucella abortus*, as well as BCG and yeast extracts (zymosan and glucan). (44, 46, 54a, 206a, 206b, 507, 508, 953)

Kuschnier and Thomas stated: "In a sense the involvement of the RES by a tumor might be compared to the phenomenon of RE blockade. . . . If animals are given injections of colloidal metals or dyes, which are phagocytized and load the cells, for 14 to 16 hours they are exquisitely susceptible to infection with minute doses of staphylococci, streptococci or pneumococci." (415) These findings suggest that the deaths of some of the patients with extensive cancers who succumbed to concurrent infections within a few days were due to the overwhelming blockade of the RES by sudden necrosis of large quantities of tumor cells.

Discussion

In contrast to the benefit derived from most types of bacterial infections, the evidence assembled indicates that with few exceptions concurrent viral infections seem to enhance the growth of a primary or its metastases. It is now recognized that viral infections are apt to depress rather than stimulate RE function. However, a few investigators such as Belisario, Milton and Pack have used vaccinia or rabies vaccines in the treatment of malignant melanoma or skin cancer with some apparent benefit. (30, 543, 622)

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Unfortunately, until recently very few investigators have considered whether some of the conventional modalities given to cancer patients might also further deplete their already exhausted immunological mechanisms. One of the first was Zacherl who observed in 1930 that not infrequently rather active growth of cancer of the cervix followed large doses of x-ray given at one sitting, while smaller doses appeared to produce a more immediate effect in causing tumor regression. Zacherl believed that with the larger doses the increased growth was caused by too extensive damage to the RES. He concluded: "... By careful adjustment of dosage, as regards time, intensity and wave length, it is hoped to give the best possible chance for the RE cells to take part in the process of defense and healing." (953)

It is now recognized that small doses of divers agents such as zymosan or glucan (67, 68, 206a, 206b), bacterial vaccines (44, 580-583k); or BCG (45, 46) can stimulate, while larger doses may inactivate or block RES function. Thus in analyzing the effects of various types of concurrent infections in the present study, it was found that those which usually stimulate the RES such as erysipelas or staphylococcus were far more effective in controlling cancer than those such as viral infections, chronic tuberculosis or fulminating septicemia which repressed or overwhelmed the RES.

Following this introduction the actual cases of concurrent infection are given in brief abstracts. For those wishing more complete reports, the detailed histories are available at the Cancer Research Institute and will be published as an Appendix if sufficient interest warrants it.

It is hoped that the data assembled here for the first time may stimulate more intensive research in this country and abroad so that many effective microbial products may be developed, not only from bacteria but also from yeasts or other organisms. These may now be used with far greater validity since so much has been learned concerning the possible mechanisms of action and the more effective technics of administration, which was unknown 90 years ago when Coley and others first attempted to utilize bacterial infections or their vaccines empirically in the treatment of cancer.

The significantly greater effectiveness of streptococcal and staphylococcal infections suggests the need for concentrating more research on these organisms at first, and since many of the infections which were salutary in their effects were probably mixed infections, it would seem wise to try different combinations to see if they may act synergistically.

The disadvantages of indiscriminate use of antibiotics discussed above should be further emphasized not only for surgeons but also for pediatricians and physicians generally.

Radiologists should be encouraged to use bacterial products as a means of increasing the radiosensitivity of the tumor while protecting the patient's hematopoietic, lymphoid and reticuloendothelial tissues.

Further studies are necessary to indicate how best we may utilize microbial products as host-stimulating adjuvants to surgery, i.e., prior to and following complete or partial removal of primary, recurrent or metastatic lesions, while conserving the lymphoid tissues wherever possible as an essential part of the cancer patient's defenses against tumor cells which remain or which already have disseminated.

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Such combined therapies will make possible less mutilating operations and thus encourage patients with early cancer to seek medical advice promptly rather than postponing such consultation due to fear of more radical procedures.

Since certain bacterial infections or their vaccines tend to stimulate wound healing and regeneration of bone dramatically, surgeons should be encouraged to administer them before and directly after whatever surgical procedure is required, in order to hasten recovery while lessening the chance for recurrence or metastases.

At present sophisticated bacteriological research is being carried out in several laboratories as a result of the studies initiated by the Cancer Research Institute.* These studies are directed toward preparing bacterial extracts from which the toxic fractions have been eliminated, while retaining their host-stimulating and tumor-inhibitory properties. Okomoto and his group of Japanese investigators have worked with streptococcal extracts since 1955 and their work is being followed with interest. (401-403; 604-607). Another Japanese product derived from streptococci is Pacibanil which induces interferon in mice (519a).

Other vaccines presently available include Pseudogen (from *Pseudomonas aeruginosa*) made by Parke Davis, Warner Lambert, Detroit, Michigan; Novo-Pyrexal, a lipopolysaccharide from *Salmonella abortus equi* developed by Otto Westphal, M.D., Ph.D., in Freiberg, West Germany; Staphage Lysate (SPL), prepared from staphylococci by Delmont Laboratories, Swarthmore, Pa.; and mixed respiratory vaccines, made by Hollister-Stier Laboratories, Spokane, Washington.

In an attempt to prevent life-threatening septicemias occurring in a large burn unit in Wisconsin, Dr. Burton A. Waisbren began administering a mixed bacterial vaccine made in his laboratory. This included among others *pseudomonas* (8 strains), *E. coli*, *Serratia marcescens* and *staphylococcus*. Such treatment worked, eliminating the need for isolating these patients, and appearing to promote healing. Waisbren then began treating his cancer patients with this vaccine, with encouraging results. (908)

Patients receiving vaccine therapy now and in the future may often be handled on an out-patient basis in "injection clinics" or in their physician's offices, thus releasing hospital beds and reducing the cost of treatment.

Much further research is needed to determine optimum duration of therapy in various types of tumors and at different stages of the disease as well as in various age groups.

Until bacterial products are available for general use in the United States, which will take far more time now due to F.D.A. regulations governing research of this type, some investigators may wish to emulate the ancient physicians. In the 18th century it was customary to establish "issues" on each of the four limbs, after operations for the removal of a cancer, with the object of preventing recurrence, and under the influence of similar ideas operative wounds were prevented from closing by first intention so that "laudable pus" might develop. Williams, in citing these observations of 18th century physicians stated that it is probable that such methods did exert some deterrent influ-

*Founded in 1953 as New York Cancer Research Institute (name changed 1973 due to international scope of its program.)

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ence on the disease. Wyeth, Coley and DaCosta in this country and several surgeons in Europe in the 19th and early 20th century actually inoculated streptococci in the region of the tumor or in the wound at the time of surgery. The experimental work of Havas (320) and Christensen (108, 109) indicates that such procedures may be extremely effective in killing tumor cells and preventing metastases.

The recent extensive work on interferon and prostacyclins suggests that certain bacterial infections or their vaccines not only stimulate the RES and cellular immunity, but also increase the production of interferon and prostacyclin in patients, thus increasing their immune competence through many different mechanisms. (References are given at the end of the discussion of interferon.)

Interferon, discovered by Isaacs in 1957, is a naturally occurring antiviral substance produced by host cells following exposure to a wide range of infections or inactivated viruses. (426a) It is a relatively stable protein of low molecular weight which inhibits most animal viruses but this property is essentially restricted to cells of the species from which the interferon was derived. (426a)

Ho et al were among the first to find that interferon can be induced by other substances besides viruses, for instance bacterial endotoxin. This presents a new parameter of the biological activity of endotoxin. (331) Other inducers include synthetic polymers resembling RNA: poly-inosinic-poly-cyridilic acid (poly: IC) and certain plastics such as pyran copolymers, as well as statocolon, a double stranded RNA that comes from the penicillium mycophage.

There are two ways in which interferon may be used: exogenous administration or stimulation of endogenous production. Exogenous interferon is rapidly cleared from the blood. Repeated injections of interferon inducers usually result in a diminishing interferon response by the host. Perhaps now and in the future one may try combining the exogenous administration with injections of interferon inducers (bacterial vaccines). Optimum timing and dosages need to be evaluated. Some investigators gained the impression that underdosage or premature cessation of interferon administration exacerbates the progress of AKR leukemia in mice.

Interferon has shown encouraging results in treating severe herpes infections in immunosuppressed patients with lymphoma or congenital immune deficiencies.

Stinebring and Youngner reported that endotoxin from *Brucella abortus*, *Escherichia coli*, *Salmonella typhimurium* and *Serratia marcescens* all induced interferon. *Brucella abortus* produced the maximum activity at 12 to 14 hours, while with *Serratia marcescens* and *Salmonella typhimurium* it appears much earlier. (952) Repeated exposure to endotoxin reduces the responsiveness of animals to subsequent injections of endotoxins, but prior infection with *Mycobacterium tuberculosis* (BCG) increases the reactivity of the host to endotoxin when measured by interferon response. (952a)

Singer et al studied the effects of a number of commercially available bacterial vaccines and allergenic extracts as regards induction of interferon in mice. They found that interferon was detected when the intravenous route was used and in certain instances after subcutaneous administration. The time of appearance and the duration of the interferon production were similar to those reported for endotoxin. They con-

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cluded that "a new activity, the induction of interferon, has been found for certain of these vaccines and extracts." (797)

Interferon-containing preparations enhance phagocytosis. (342a)

Homma and his colleagues have isolated a component from *Pseudomonas aeruginosa* (OEP) which possesses remarkable biological properties, showing antitumor and interferon-inducing activities. (850)

In planning interferon therapy of cancer patients now and in the future we must learn to know what factors may augment levels of circulating interferon. Siegel noted that administration of ascorbic acid to mice in their drinking water caused augmented levels of circulating interferon after stimulation with murine leukemia virus. (795, 795a) In another study they found enhancement of interferon production by poly (rI) poly (rC) in mice fed ascorbate-supplemented diets. (795a)

Among the factors which can inhibit the synthesis and antiviral action of interferon are stress, steroids, antimetabolites and carcinogens. (250a) Kilbourne et al reported that it seems possible that endogenous adrenal corticoids may influence the dynamics and outcome of infection *in vivo*, depending on the balance of their effects on viral synthesis and on the synthesis and action of interferon. (379a) Thus the stress of trauma or surgery, or various forms of psychic stress may, through their stimulation of endogenous adrenal corticoids, have a deleterious effect on interferon synthesis. (250a)

Over the years, work has proceeded on the basic biology of interferon and on ways of producing interferons. Several different interferons have been purified to apparent homogeneity.

It is now possible by "genetic engineering" to produce large amounts of interferon by cloning in bacteria (*Escherichia coli*).

Interferons can slow cell division, enhance natural killer cell activity and by acting on T cells they can modulate immune responses. Interferon can restrain the growth of various tumors in mice even if they are not virus induced.

The application of all of this information to clinical medicine has depended on the outstanding work of Kari Cantell in Finland, who perfected methods of making interferon from human buffy coat leucocytes and of processing and purifying it for clinical use.

Strander and his colleagues in Stockholm have now used interferon on patients with osteogenic sarcoma, as an adjuvant to standard surgical or radiation therapy, resulting in decreased incidence of metastases and prolonged survival. (227)

This group has also reported quite dramatic remissions in a small number of multiple myeloma patients following interferon therapy. (527) Gutterman has confirmed these findings, including the fact that patients in an advanced stage of the disease do not respond (to be published). Gutterman also noted regression of metastatic breast cancer nodules when treated with intramuscular interferon. It seems that interferon possibly may prove useful in the management of malignant disease, though much more work is needed to find out how best to use it. (227)

Pertinent references to recent interferon research are: 226b, 250, 250a, 290, 298a,

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298b, 303a, 305a, 331, 379a, 424, 426a, 527, 633a, 662a, 795, 795a, 797, 799, 814, 825, 834a, 837a,b,c,d, 849, 850, 952, 952a.)

Summary

The present study comprises all the data available on the effect of various infections on cancer. In addition to these data, during the past 27 years end-result studies of various types of cancer treated by bacterial toxin therapy have been made. Some of these have been published, others are in press. (256-259; 542b; 583-583k, 650-652)

When this study was begun little was known about mechanisms of action of microbial infections or vaccines. Interferon and the prostaglandins had not yet been discovered. The role of iron as an important regulatory factor in host-parasite interactions had not been recognized. All these findings help us to understand how the remarkably beneficial effects of infections and endotoxin and vaccines could occur in cancer patients.

It would seem that now a great deal more coordinated clinical, as well as experimental, research is warranted on various aspects of this most hopeful approach to the cancer problem.

SERIES A, GROUP 1, DETERMINATE SUCCESSES, TRACED 5 TO 46 YEARS: 37 CASES

Type of Tumor:

- 11 carcinoma: #8, 11, 12, 16, 17, 18, 20, 22, 29, 31, 33
- 7 sarcoma of soft tissues: #2, 3, 4, 6, 9, 21, 34
- 5 neuroblastoma: #13, 14, 25, 28, 30
- 7 malignant melanoma: #1, 15, 23, 27, 35, 36, 37
- 2 hypernephroma: #25, 26
- 2 chorioepithelioma: #7, 32
- 3 bone sarcoma: #5, 6, 24
- 1 retinoblastoma: #10
- 1 lymphosarcoma: #19

Type of Infection:

- 14 suppuration and/or wound infection: #6, 8, 11, 13, 15, 17, 20, 23, 24, 27, 31, 34, 35, 37
- 10 abcess and/or sepsis: #7, 14, 15, 16, 21, 29, 33, 34, 36
- 9 streptococcal: 5, 9, 12
 - 6 erysipelas: #1, 3, 4, 5, 9, 12
 - 3 other than erysipelas: #2, 10, 19
- 3 urinary tract infections: #21, 26, 28
- 2 *Pseudomonas aeruginosa*: #31, 34
- 1 pneumonia, lung embolus, pleural effusion: #21 (also had food poisoning)
- 2 otitis media or mastoid: #25, 34
- 1 pyoderma: #30 (also had varicella)
- 1 peritonitis: #18
- 1 pertussis, rubeola: #13 (also had bullous urticaria and suppuration)
- 1 meningitis: #9 (also had erysipelas)
- 1 bronchitis, high fever: #25

(Note: Many of the patients with suppuration and abcesses may also have had streptococcal or mixed infections but this was not proven bacteriologically.)

Site of Primary Tumor:

- 8 head and neck: #3, 5, 9, 10 (eye), 16, 19, 34, 35
- 5 colon and rectum: #11, 17, 22, 29, 33
- 5 sympathetic nerve tissue:
 - 2 adrenal: #25, 30
 - 1 hypochondrium: #13
 - 1 lumbar region: #28
 - 1 cervical region: #14

SERIES A, GROUP 1, DETERMINATE SUCCESSES

- 14 soft tissues: #1, 2, 3, 4, 5, 6, 9, 12, 15, 21, 23, 27, 34, 35
- 2 uterus: #7, 32
- 2 ovary: #8, 20
- 2 kidney: #25, 26
- 2 bone: #6, 24 (humerus, femur)
- 1 prostate: #31
- 1 intra-abdominal and pelvis: #21
- 1 omentum: #18

Factors Other Than Concurrent Infection Which May Have Affected Host Resistance:

Surgery:

Prior to or concurrent with infection

- 12 incomplete removal: #3, 6, 7, 9, 12, 15, 17, 22, 23, 26, 31, 33, 35
- 4 explored: #8, 18, 25, 29
- 7 biopsy: #18, 19, 25, 28, 30, 31, 34, 35

Following infection

- 2 excision of remains of growth: #4, 8
- 2 biopsy of metastases: #27, 30
- 1 excision of metastasis: #15

Stimulated Systemic Resistance:

- 2 bacterial toxin therapy (Coley toxins): #19, 24
- 3 transfusions: #21, 25, 26
- 2 confinement: #18, 21
- 1 cutaneous eruptions: #13
- 1 tagged antibodies: #27
- 1 dose BCG #37

Stimulated Local Resistance through Induced Inflammation:

- 9 small or moderate amounts of radiation: #13, 14, 15, 16, 19, 24, 27, 29, 34
- 1 injections of Fowler's solution: #2
- 1 injections of alcohol: #7
- 1 local heat: #2
- 1 mud pack poultices: #11
- 1 scraped primary lesion off while swimming: #23

SERIES A, GROUP 1, DETERMINATE SUCCESSES, BRIEF ABSTRACTS (37 CASES)

These 37 inoperable microscopically proven cases developed pyogenic infections spontaneously, causing regression. The patients were traced from 5 to 45 years after onset. In 22 of these 37 cases metastases were present and in six others were recurrent when infection developed. The name in parenthesis following the case number denotes the physician or hospital handling the case or publishing the report. Bibliography reference numbers appear at the end of each abstract. The years traced after onset are given to the right of each case.

1. (*Bruns*): Female, aged 47; recurrent inoperable malignant melanoma on chest wall, with axillary metastases; primary growth excised, axilla cleared; rapid recurrence; *severe erysipelas spread over greater part of body lasting 3 weeks; recurrent growth entirely disappeared; no further recurrence or metastases; entirely well when last traced 1889.* (56; 72; 125; 193; 257; 383; 567; 821). 9½ yrs.

2. (*Wyeth*): J.W.P., male, aged 33; inoperable spindle cell sarcoma abdominal wall 10 × 15 × 9 cm. adherent to muscles; loss of weight and strength; exploratory laparotomy; 5 minims Fowler's solution injected daily into mass for 2 weeks; June 1884: *tumor and overlying tissues became infected, apparently streptococcal, suppuration, high fever; warm local applications made; extensive growth entirely disappeared; no recurrence,* alive and well 1901. (138, Case D. in Table of erysipelas cases); 583i; 945; 946; 949). 17 yrs.

3. (*Bull*): F.K.S., male, aged 29; recurrent inoperable round cell sarcoma neck; onset, 1880; 4 operations, final one incomplete; October 1884; 2 *attacks facial erysipelas; sarcomatous granulations completely disappeared; no further recurrence;* traced by W. B. Coley in 1891, in good health. This case led Coley to induce erysipelas in cases of inoperable cancer and to his development of the Coley toxins. (124; 125, Case 25 in Table; 344; 579; 590). 11 yrs.

4. (*Biedert*): Female, aged 11; extensive recurrent inoperable very vascular round cell sarcoma of left tonsil, involving posterior half of pharynx, left half of tongue (an ulcerated mass), palate, nasopharynx, inner canthus of both eyes, both orbits; right eye was a fungating mass of growth; foul odor from ulceration; attacks of asphyxia, deglutition very difficult, condition almost moribund; intense dyspnea; finally unable to take any food, tracheotomy performed; November 17, 1884, *erysipelas developed at site of ulcerated mass over right eye, lasted 6 days, fever to 40° C.; tumor masses shed away in all directions, ulcers rapidly healed; appearance of face,*

SERIES A, GROUP 1, DETERMINATE SUCCESSES

mouth normal; respiration, deglutition, phonation normal, appetite excellent; all the extensive growths disappeared except for two small nodules the size of peas in the scar over the left eye and nose; these were excised. No further recurrence, remained in good health; marked stenosis of throat due to contraction of cicatrices following regression. Last seen in good health April 1898, only complaint was some eczema of forearm. (40; 72, p. 433; 125; 141; 265; 307; 344; 567; 583; 723; 724; 725; 727; 821; 918).

14 yrs.

5. (*Gerster*): Young girl; twice recurrent inoperable sarcoma middle of leg; mid-thigh amputation, recurrence in stump several mos. later; hip-joint amputation; 2nd recurrence in cicatrix; extensive bleeding cauliflower mass; 1885, *erysipelas in region of recurrence; large masses of tumor sloughed off, "all traces sarcoma disappeared"*; alive and well, no further recurrence, 1901. (946, p. 986, p. 383).

16 yrs.

6. (*McCosh*): M.J.D., female, aged 32, inoperable small round cell sarcoma humerus; onset February 1892, shortly after injury to shoulder; disarticulation 4 weeks after injury; growth had infiltrated acromion process and soft tissues (mass size large hen's egg remained); cavity packed, flaps drawn loosely; March 1893 *wound suppurated freely for 3 mos., complete regression, no recurrence*; well until sudden death from sepsis following abortion, 1897. (132, pp. 176-177, 544-545; 483; 484).

5 yrs.

7. (*Von Franqué*): F.M., female, aged 25; malignant chorioepithelioma of uterus, post-partum; June 15, 1897; curettage, alcohol injected into uterine cavity; *marked sepsis, fever, chills, lasting 11 days*; 2nd curettage 18 days later; *no trace of malignant elements which had been present prior to infection*; had 2 more children; in good health when last traced 1903. (268; 340; 344; 349; 583j).

6 yrs.

8. (*Codman*): Mrs. R. U., female, aged 32; inoperable papillary cyst adenocarcinoma of ovary with diffuse wart-like metastases over whole peritoneum; condition at first thought to be pelvic abscess; June 30, 1900: incision in vagina, papillocystic material curetted, drainage established; explored 9 days later; large inoperable pelvic mass found, no attempt at removal of primary or metastases; *vaginal sinus persisted 10 yrs., discharged pus and occasionally necrotic tumor tissue; tumor grew, ulcerated, but general condition improved*; patient returned each yr. begging for operation; finally third operation, 10½ years after first; huge adherent pelvic tumor present, *all metastases had disappeared*; tumor mass removed together with rectum; artificial anus made; patient recovered, *remained in good health, entirely free from disease 1936*; died March 6, 1944 chronic myocarditis. (117, Case 1; 583j).

44 yrs.

SERIES A, GROUP 1, DETERMINATE SUCCESSES

9. (*Ramon y Cajal*): Male, aged 40; inoperable round cell sarcoma, involving entire right naris and nasopharynx; attempt at removal abandoned because of severe hemorrhage (tumor very vascular); 3 days after incomplete operation *severe erysipelas, high fever for 9 days, meningitis; complete regression remains of growth by suppuration*; thereafter patient's personality changed radically, mind affected by meningitis; no recurrence of sarcoma; well 1911. (691).

Over 10
yrs.

10. (*Stallard*): Male, aged 4; recurrent retinoblastoma, primary in left eye; enucleation; recurred in right eye; further operation refused; 1904: developed *very severe scarlet fever, during which right eye gradually cleared*; no further recurrence; married, had two sons (both had bilateral retinoblastoma); alive and well 1934. (822).

30 yrs.

11. (*Most*): Male, aged 57; recurrent extensive inoperable carcinoma rectum; general condition poor, considerable weight loss; inoperable apple-sized mass present when first seen, April 1918; symptomatic treatment only; appeared better, May 1918, so x-ray therapy tried; general condition continued to improve, so palliative surgery attempted, June 28, 1918; tumor firmly fixed to bladder incompletely removed, base cauterized; good recovery, except for complete bladder paralysis; recurrence on perineum apparent 20 mos. later, of rapid growth, soon made sitting, standing or walking painful; bedridden; again seen summer 1920, extremely debilitated, dreadful pain; *bleeding and profuse ichorous suppuration from growth in anus*; hospitalization and further palliative surgery advised, refused; relatives then applied wet mud packs; became psychotic September 1920, condition hopeless; *further poulticing; growth gradually but completely regressed, complete recovery, resumed occupation*; 1922, fell, fracturing femur, not due to metastases, complete healing; no further evidence of disease, alive and well October 1927. (237, pp. 387-389; 258; 563).

10 yrs.

12. (*W.B. Coley*): C.K., male, aged 35; squamous cell carcinoma (grade II) left foot developed 1923, 6 yrs. after x-ray therapy for severe ring worm infection both feet; extensive inoperable metastases in inguinofemoral nodes; radium pack to left groin, several excisions plantar surfaces both feet; final operation December 11, 1929, growth incompletely removed; when slough came away suspicious area remained, biopsied again, showed squamous carcinoma; December 15, 1939 *severe erysipelas infection on calf of leg, radiating to lesion of foot and up thigh to groin, forming several residual abscesses which were incised*; after recovery from infection left foot amputated as a precaution; two I.V. injections Coley toxins then given; no further recurrence or metastases; November 1946: vagotomy and posterior gastro-enterostomy for chronic perforating duodenal ulcer; in very good

SERIES A, GROUP 1, DETERMINATE SUCCESSES

general health except for mild coronaries, 1951, 1956; in September 1961, following strenuous European trip, and severe virus infection (influenza) chest films revealed extensive cancer involving both lungs and mediastinum (apparently a second primary) condition inoperable; palliative cobalt therapy caused severe radiation sickness; death March 4, 1962. (123; 528; 589).

32 yrs.

13. (*Debré*): Female infant; inoperable neuroblastoma, primary in right hypochondrium first noted in June 1930 at 7 months; palpebral hematoma and metastases to supraorbital region appeared at 8 months; regressed spontaneously a month later (child was with "wet nurse"); primary mass increased slowly; 7 x-ray treatments given at age of one year, no effect; general health not affected; at the age of two *pertussis and rubeola*; no complications; at 2½ a small metastatic nodule appeared on left knee and that summer another on her back; at this time she developed *urticarial rash on legs* (considered due to eggs); nodule on left knee biopsied October 26, 1931; *further extensive bullous urticaria with pruritis and suppuration*. no treatment given; new metastatic nodule appeared on right thigh, November 1931; *thereafter disease remained stationary; by 1935 abdominal mass had decreased 1/3 to size of fist; tumor on back remained hard, very mobile, but was regressing; no new nodules developed, abdominal mass finally disappeared* married, had two children; during second pregnancy, 1961, small uterine fibroid detected; following confinement it regressed and was not evident at subsequent examinations, in excellent health 1977. (185; 259; 589; 889).

46 yrs.

14. (*MacFarland & Sappington*): A.C., female, aged 7; inoperable neuroblastoma, apparently primary in cervical region, with multiple pulmonary metastases; onset, at 5½ years, cervical lymphadenopathy, diagnosed as tuberculous adenitis; x-ray (5); 3 wks. after last treatment, *pharyngeal abscess, w.b.c. 6,200-7,400*; February 1932, tonsillectomy, *abscess opened, slight fever*; general condition improved, but chest films showed mottling in both upper lobes; tumor in cervical region excised May 4, 1932; *pathologist reported it was in process of maturing into ganglioneuroma; slight postoperative fever for 2 wks.; 2 more x-ray treatments as prophylactic; complete regression lung metastases, well, symptom free*, November 1934. (491).

Over
5 yrs.

15. (*Memorial Hospital*): N.H., male, aged 40; malignant melanoma left shoulder, metastases to axilla, chest wall and infraclavicular region; (date of onset not recorded); had capillary and pedunculated hemangiomas, nevi over entire body; "mole" excised from left shoulder December 1931; concurrent *macular skin eruption* on trunk, extending to extremities;

SERIES A, GROUP 1, DETERMINATE SUCCESSES

axillary dissection March 18, 1932; *postoperative wound infection (abscess, slight fever)*; x-ray then given, metastases to chest, excised November 23, 1932; another May 9, 1933; 3 more September 1, 1933; *most of remaining nodules on scalp and breast regressed spontaneously*; further excision May 1, 1934, October 9, 1934, March 28, 1935; axillary dissection April 23, 1935, very unusual dark metastatic growth; *complete spontaneous regression* November 1936, *infection, inflammation; no further evidence disease thereafter*; alive and well 1973, working every day; died 1976 at 86. (257; 528; 589).

About 45
yrs.

16. (*Janker*): Male, aged 50; inoperable cylinder cell carcinoma larynx, lymph node metastases at angle of jaw; prolonged radiation produced temporary regression; further metastases right sternocleidomastoid, posterior to clavicle; further x-ray given, some decrease in size; *developed enormous abscess gluteal region January 1938, very high fever; general condition very much affected; during convalescence, metastases regressed very rapidly and completely, no further evidence disease*, alive and well 1961, (356; 589).

23 yrs.

17. (*Snyder, Clark & Rubini*): D.B., female, aged 62; inoperable annular ulcerating adenocarcinoma sigmoid colon, penetrating to small bowel, bladder and uterus, with metastases to regional lymph nodes; family history was then negative for cancer, but an only son developed adenocarcinoma of cecum and ascending colon 19 years later, (see below case 33); patient had mild rheumatoid arthritis; late in 1938 constipation developed and weight loss (30 lbs.); exploratory laparotomy, January 20, 1939; obviously inoperable lesion involving 8 cm. of mid-portion of sigmoid with palpable nodes in mesosigmoid; because of bleeding and impending obstruction, palliative incomplete resection was done; *post-operative wound infection, fever to 102° F. for 10 days, leukocytosis (15,750 wbc); slow recovery, (no antibiotics); remains of growth completely regressed, no further evidence disease*: died other causes at 78 in 1953. (258; 589; 812).

14½ yrs.

18. (*Levine and Weiner*): Mrs. G.M., female, aged 34; diffuse inoperable adenocarcinoma, apparently primary in omentum with metastases in peritoneum, mesentery, ovary, liver, developing soon after birth of first child; exploratory laparotomy, several peritoneal implants taken for biopsy, attempted liver biopsy (extensive friability, marked bleeding); prognosis hopeless; March 6, 1940; *immediate postoperative course very stormy due to peritonitis, (temperature persistently elevated, pulse poor, abdomen markedly distended)*; *all trace metastatic growths disappeared*; normal menstruation in 6 weeks; became pregnant 3 years later; as precaution pregnancy terminated by total hysterectomy, bilateral oophorectomy; no microscopic evidence of disease. Alive and well 1955; not traced thereafter. (447, 583j, 589).

15 yrs.

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19. (*Plaut*): J.P.G., male, aged 23; large lymphosarcoma right submaxillary region; onset, January 1942; increased to size of baseball in less than 2 weeks; patient admitted with perforated peptic ulcer for emergency operation January 22, 1942, ulcer on pre-pyloric stomach plicated; 12 days later developed *pulmonary infarct from embolus (hemolytic streptococcus, fever 103°-104° F.; tumor disappeared completely in 2 days; recurred 2 weeks later; no removal attempted, just incisional biopsy; 17 doses Coley toxins (Parke Davis XIII) April 1942, i.m. and i.v.; deep x-ray therapy then given (6 or 8); recurrence disappeared; no further evidence disease, gained 86 lbs. in next 10 yrs.; gastric symptoms persisted; partial gastrectomy about 1952; weight declined, felt better; June 1966, retinal hemorrhage caused blindness right eye; no evidence disease, in good health June 1977. (583; 589).*

Over
35 yrs.

20. (*Gaudrault*): A.S., female, 26, metastatic inoperable bilateral papillary cyst adenocarcinoma ovaries, extensive peritoneal implants over entire pelvis; onset, November 1935, discomfort lower abdomen, back, legs; symptoms increased markedly fall 1939, ascites, cachexia; abdomen distended, tender; exploratory laparotomy, November 1939, 2 liters ascitic fluid evacuated, large papillary growths both ovaries, extensive peritoneal implants entire pelvis, no attempt at removal, biopsy taken; intestinal obstruction December 1939; tapped 63 times over 2½ years, 5,000-10,000 cc. each time, maintained on morphine (to 30 mg. every 3 hours); weight decreased to 80 lbs.; patient demanded 2nd operation, June 1, 1942; appearance altogether different, all metastatic papillary growths were encapsulated in large mass to left and 2 smaller ones to right, all adherent to adjacent organs, rectum, uterus, bladder; growths dissected, removed with great difficulty, except for 4 cm. portion in right fossa, some contents spilled in abdomen, removed with care; *postoperative fever (99°-104° F.) for over 3 months, also suppuration and discharge from abdominal sinus; 2 transfusions, no more morphine; complete recovery, no further evidence disease, alive and well in April 1980, except for some arthritis, Paget's disease and hypertension. (279; 280; 583k; 589).*

Over
45 yrs.

21. (*Memorial Hospital*): Mrs. V.A., female, aged 30; inoperable extensive spindle cell sarcoma pelvis (date of onset not recorded); known to have had tumor 8 cm. in diameter in 1940 so had her children by Caesarian section, 1940, 1944; aspiration biopsy, November 1944; exploratory laparotomy and right salpingo-oophorectomy revealed tumor 12 × 6 × 5 cm. in right pelvis, severe bleeding, 1,500 cc. blood transfused, patient nearly moribund from shock; January 23, 1945: *postoperative pneumonia, pulmonary em-*

SERIES A, GROUP 1, DETERMINATE SUCCESSES

bolus, pleural effusion, septicemia and pelvis abscess with fever to 106° F., infection lasted three months; she survived these complications, but prognosis appeared hopeless, palliative x-ray given spring and fall 1945 totalling 3,750 r to each of six portals and 4,000 r to two other portals; tumor seemed larger during September, but by November it had regressed 75%; several attacks urinary tract infection, January to March 1946 with spiking fever to 104° F., chills and acute pain; four episodes food poisoning, 1946-1947; virus pneumonia fall 1953; disease regressed completely; no recurrence, in good health for about 15 years, then colon resected for diarrhea due to radiation changes; 1978, nephrectomy for radiation damage to kidney; developed osteoporosis; hip fracture fall 1979, alive and well 1980. (528).

35 yrs.

22. (Fallis & Brennan): J.D.K., male, aged 41; extensive fungating inoperable adenocarcinoma of the left half of transverse colon with metastases to abdominal wall at sites of fistulae; 10 lb. weight loss in 2 weeks, pain; September 1941 explored, mass considered due to ruptured diverticulum with abscess formation; pus aspirated, cigarette drains inserted, sulfanilamide in wound; stormy course, pain, nausea, vomiting; condition deteriorated, bedridden; 2nd sinus opened, discharged feces, normal bowel movements ceased; indurated elevated area about old scar and fistulae 12 × 20 cm. biopsied February 27, 1942, revealing metastatic adenocarcinoma invading subcutaneous tissues with massive necrosis affecting large areas of tumor; tumor mass superficial to skin margin about scar and sinus tract excised, base arising in colon untouched; condition worse, lost 24 lbs. in next 3 months; by July 1, 1942, when wound had healed he began to improve, gained 62 lbs., colostomy closed that fall; extensive carcinoma regressed completely, n.e.d. thereafter, in excellent health; small epigastric hernia repaired, appendectomy September 6, 1957; wedge resection right middle lobe for indeterminate lesion which proved to be old infarct, 1963; operated for small bowel obstruction: 1963; large ventral hernia repaired, 1966; barium enema then showed no lesions, chest films negative except for enlarged heart; cholecystectomy, February 1967; overweight: weighed 225 lbs., height 6 ft.; remained in good health; died heart attack March 29, 1977. (237, p. 396-399; 589).

35½ yrs.

23. (Urban): E.W.H., male, 27, of Hawaiian Islands; recurrent, metastatic melanoma of left axilla and fascial plane. primary unknown; onset, small lesion on dorsum lt. hand present Spring, 1946; scraped it off while fishing late May 1946; week or so later swelling noted in lt. axilla; no evidence infection but penicillin given, no effect; August 20, 1946, large mass removed, "broken down nodes" removed involving subpectoral group (in Hawaii); pigmented material noted below the lesion. Tiny macule in lt. retina present (regarded as benign melanoma); radical lt. axillary dissection at Memorial Hospital; areolar tissues in fascial plane between latissimus

SERIES A, GROUP 1, DETERMINATE SUCCESSES

dorsi, subscapular muscles and chest wall densely infiltrated by black pigment; several firm nodes excised from axilla up to costoclavicular ligament, some disease remained; (nodes revealed only benign hyperplasia, tissue in fascial plane: rather low grade malignant melanoma); *wound drained through stab wound; became infected when patient took bath, staphylococcus*; deferred marriage 3 yrs., had 2 children; in excellent health, N.E.D., February 1980. (93; 528).

35 yrs.

24. (Memorial Hospital): E.B., female, aged 24; massive reticulum cell sarcoma right lower femur, regional groin metastases; (onset June 1946) considered inflammatory or cartilage; fell on knee; local physician opened joint, told her to exercise it a lot; swelling, increased pain; another operation; manipulation tried; December 1946 metastases in right groin; x-ray given, 3 over groin (slight regression), 5 over knee, (1600 r each); swelling, pain increased; knee 3 times normal size; *medial incision; area dirty, infected, lateral aspect red, fluctuant*; preliminary diagnosis synovioma, with inguinal node metastases, prognosis hopeless; x-ray showed extensive soft tissue mass in right inguinal region; extensive soft tissue mass in knee region, collection of fluid in joint space and extensive involvement of femur; because condition was regarded as hopeless, discharged untreated; tissue removed at former operation reviewed by Stewart (reticulum cell sarcoma); March 24, 1947: lower extremity tremendously edematous and tumor area ulcerated when combined toxins and x-ray begun; (affected limb 61.5 cm., normal 37 cm.); x-ray to groin, (1500 r), anterior right thigh, (1500 r); knee (8000 r); Coley toxins concomitantly, 22 in 27 days, five in tumor, rest i.v.; reactions averaged 102.2°F. to 103.6°F. (maximum 105°F.); improvement evident a wk. after treatment started; in 3 wks. abdominal mass had decreased 50%, edema of leg continued to recede; discharged markedly improved April 26, 1947; patient became engaged to be married; further toxins June 3, 1947; 15 i.v. in 22 days, febrile reactions averaged 102.8°F.-104°F. (maximum 105°F.); further x-ray July 1946; *improvement continued, complete regression*; June 1948, married; three children, 1950, 1951, 1953; in excellent health, 20° range of motion in knee, able to carry out household duties; no further evidence disease 1976. (122, Case 24; 528, 546b, 589).

30 yrs.

25. (Goldring): G.S., male, aged 4 months; inoperable neuroblastoma right upper kidney region extending into right upper abdomen to liver, numerous metastases to liver, right proximal humerus, skull, both periorbital regions, causing extensive proptosis; *mild otitis, pharyngitis*, March 1947; wbc., 15,500; sudden bilateral hemorrhages of eyelids, very anemic; 9 transfusions whole blood, April to July 1947; x-ray to kidney region, April 1947 (1,200 r); *concurrent fever*; May 1947, again had rhinitis, *fever to 101°F.*; May 24, 1947, explored; extensive liver involvement found, some soft, some hard nodular metastases; mass extended from kidney to liver; biopsy wedge taken

SERIES A, GROUP 1, DETERMINATE SUCCESSES

from liver; May 1947, further x-ray to kidney region (700 r); proptosis became worse during radiation; final transfusions July 1947; *striking improvement by August 1947, continued steadily; another upper respiratory infection, April 1948: high fever, bronchitis; primary and metastases all disappeared*; no evidence of disease by September 1948; grew normally, in excellent health thereafter; alive and well until sudden heart attack fall 1978, in coma 2 wks., died December 1978. (259; 288; 589).

31 yrs.

26. (Prentiss): C.B.L., female, aged 63; hypernephroma, Grade IV, of the right kidney, with multiple large bilateral pulmonary metastases; onset, 1947, gross hematuria, right renal colic, weakness, pallor, moderate secondary anemia, moist rales in both lungs; round smooth movable 15 cm. mass in right flank present when admitted; *concurrent pyuria, sulfathiazole given; chill, temperature 102.5° F.*; nephrectomy was done to relieve pain and bleeding; 4 transfusions (2 before, 1 during, 2 after surgery); pathologist reported renal vein blocked by tumor; *complete recovery, 10 mos. later chest completely free of all metastatic lesions, general health excellent*; remained entirely well, n.e.d. until sudden death cerebral hemorrhage fall 1972. (237; 583a; 589; 686).

24 yrs.

27. (Vial and Callahan): V.P., male, aged 60; metastatic malignant melanoma, primary in right anterior thigh; onset, July 1948, 2 cm. pigmented nevus on thigh; September 1948, *left maxillary sinusitis*; lesion on thigh excised, March 1950; recurred, irradiated without effect; tumor mass increased with many pigmented satellite skin nodules; parahydroxypropiouquinone, radioactive iodine, radioactive copper given without effect; *groin mass became infected*; generous biopsy of this lesion, October 1951; *leukocytosis (11,350); legion remained infected, suppurated for 5 months*; 2 injections tagged antibodies against patient's own tumor then given (rabbit gamma globulin tagged with radioactive iodine); 2nd caused anaphylactic reaction, December 1951; *5 parenchymal lung metastases present prior to this then decreased in size, disappeared in 3 mos.*; patient myxedematous, required thyroid replacement, which he neglected at times; further metastases in right groin, 1953; Thio-TEPA for a month without effect; 1 more injection tagged antibodies; biopsies, October 1953, January 1954, positive for malignant melanoma; *thereafter, no further evidence of disease*; died suddenly at work, January 27, 1958, coronary insufficiency; no evidence of malignant melanoma seen at autopsy. (257, 589; 896).

10 yrs.

28. (Eyre-Brook & Hower): Female infant, inoperable massive neuroblastoma right lumbar region, derived from paravertebral sympathetic nerve tissue; hard swelling 1st noted in right lumbar muscles at 3 months, early September 1949; in next month it increased in size, with weakness of calf muscles; during early November 1949, abdominal mass on left side became

SERIES A, GROUP 1, DETERMINATE SUCCESSES

palpable, marked foot drop, some paralysis of feet; x-rays showed extensive mass deforming bladder; *concurrent cystitis (coliform bacilli and pus in urine)*: December 1949, incision biopsy; condition inoperable, large piece removed for biopsy; prognosis hopeless, discharged untreated; some urinary retention caused *cystitis during next decade; within 18 months after exploratory surgery complete regression of abdominal neuroblastoma occurred, but residual paralysis of legs remained due to compression of cauda equina, with impaired bladder functions*; this led to progressive deterioration of kidney function, death from uremia, June 1959, 10 years after onset. Necropsy revealed no abnormality in abdomen other than gross pyonephrosis, dilation of bladder and ureters; peripheral portion of extensive neuroblastoma of lumbar spine had regressed, remaining dumb bell shaped tumor in lumbosacral canal had matured into a small ganglioneuroma. (237; 238; 259).

10 yrs.

29. (*Mayo Clinic*): Male, aged 45; inoperable perforated obstructing adenocarcinoma descending colon extending into sinus tract above crest of ilium; September 1950 developed *abscess in left flank*, incised and drained twice, patient lost 40 lbs.; acute obstruction, March 1951; colonic stoma established; explored 6 months later, nodular, irregular mass found involving lower portion descending colon, solidly fixed to bony pelvis; *sinuses above crest of left ilium drained pus (strep)*; curettage of sinus yielded masses of malignant tissue; x-ray therapy (3,000r in 12 days); *sinuses healed in one month, inoperable growth disappeared*; re-explored September 1953; no evidence of lesion found; 15 cm. segment of lower bowel absent; side to side colocolostomy done; transverse colonic stoma closed November 1953, bowel function normal thereafter; regained weight, entirely well nearly 7 years; returned August 17, 1960, marked tenderness in l.l.q. of abdomen; operated August 23, 1960 found to have second primary adenocarcinoma sigmoid which was resected; *grossly had appearance diverticulitis; marked inflammatory reaction around tumor*, no evidence of perforation, nor of former lesion; remained well; later developed pulmonary emphysema; died March 28, 1979, of cerebral vascular insufficiency, acute bronchitis and pulmonary emphysema. (93; 247; 258; 589; 865).

28 yrs.

30. (*Hörnstein & Muelke*): S.K., female infant, aged 3 weeks; neuroblastoma right adrenal, multiple metastases; as newborn had "sore in oral cavity"; onset, at age of 2 to 3 weeks, mother noted small tumors subcutaneously in genital area and both hips; admitted at 3 weeks in good general condition, with numerous deep subcutaneous or subcutaneous tumors over entire trunk and proximal lower extremities (bean to pigeon egg size); a single tumor biopsied; prednisone given orally for 2 weeks (5 mg. daily); *at 3 months developed pyoderma involving head and neck regions, refractory to antibiotics*; at 3½ months trial x-ray therapy given to 1 metastasis (400 r

SERIES A, GROUP 1, DETERMINATE SUCCESSES

× 6 in 5 weeks); no apparent effect; *further course characterized only by recurrent episodes of pyoderma at intervals of about 7 or 8 weeks*, and nutritional disturbances, treated at first by dietary restrictions, then sulfonamide; all this occurred without the child's becoming essentially deteriorated or developing cachexia; 2nd biopsy showed small isolated area of necrosis; calcification in area of right adrenal became evident on x-rays; *varicella at 5½ months; "conspicuously from that time the metastases became noticeably smaller"; within a month many small nodes, especially those that had appeared last, disappeared*; during this time no therapy was given; 3rd biopsy, January, 1958, showed *completely changed picture; tumor no longer malignant, inflammatory reaction present; child appeared healthy, not retarded in any way, mentally or as to skeletal growth*; examined periodically thereafter; in excellent health at last observation, 1980. (259; 339; 567; 589).

23 yrs.

31. (Myre): Male, aged 83; inoperable carcinoma prostate (Grade 2), possible lung metastases; May 1957: biopsy, orchiectomy suprapubic cystostomy; since mass had invaded sphincter, prostate was not removed; stilbestrol; June 24, 1957: *infection right axilla (Pseudomonas aeruginosa); carbuncle incised, drained, penicillin given*; chest films September 1957 showed density in right lower lobe; May 1958 *another carbuncle in left axilla; prostate normal, hard nodules on right and left had disappeared following infections*; May 1959 *lungs clear*; that summer patient became weakened and general health declined; autogenous vaccine of *P. aeruginosa* given intradermally weekly (0.04 to 0.05 cc.) caused local inflammatory reactions, no fever or malaise; continued for over 2 years *general health improved; entirely symptom free, remained in good condition, n.e.d. until sudden death from pneumonia, June 14, 1963.* (589).

6 yrs.

32. (Hearin): J.T. female, aged 28; malignant chorioadenoma destruens of uterus with pulmonary and pelvic metastases; onset, intermittent spotting late November 1957, continued until curettage January 15, 1958; uterus size of 5 month gestation; large amount of grape-like material evacuated; considerable bleeding; 2nd curettage March 23, 1958; persistent trophoblastic tissue; *postoperative infection, chills, fever 103° F. or more for over 2 weeks, antibiotics given*; readmitted April 9, 1958; 3 × 3 cm. stony hard mass in left adnexa; metastases present in both lungs; transfusions; hysterectomy; bilateral salpingoophorectomy, April 2, 1958, large tumor present on posterior uterine wall, another large nodular mass in region of bladder extending to pelvic wall; latter could not be completely removed; *it slowly decreased in size; by August 16, 1958 the multiple nodular lesions in lungs had mostly regressed; "amazing improvement," complete regression occurred; patient entirely well 1977.* (320, 583j; 589).

Over
20 yrs.

SERIES A, GROUP 1, DETERMINATE SUCCESSES

33. (*Snyder, Clark & Rubini*): N.B., male, aged 60; inoperable, poorly differentiated adenocarcinoma of cecum and ascending colon, involving terminal ileum, with tremendous seeding of entire peritoneal cavity and omentum by metastatic lesions; (his mother had developed inoperable adenocarcinoma of sigmoid colon in 1939 and recovered following wound infection after incomplete surgery, see above, case 17); he had had moderate rheumatoid arthritis which had been quiescent for years; onset, early 1958, constipation; barium enema suggested carcinoma; exploratory laparotomy revealed tremendous seeding of entire peritoneal cavity, regional lymph nodes grossly involved, condition obviously inoperable; biopsies of primary and several nodes; thereafter increasing anorexia, large tender mass in right lower quadrant present, April 1958, when Nitromin given (20 mg. orally daily for 10 days); no leukopenia, mass decreased in size; 2nd laparotomy, April 30, 1958, to avoid incipient obstruction; growth had spread to involve loops of terminal ileum, hard studded masses of tumor in mesentery of small bowel; *considerable inflammation surrounded tumor, local infection thought to be present*; palliative hemicolectomy and bypass performed; tumor tissue remained in mesentery, peritoneal fat and along iliac crest, some were biopsied; removal incomplete; chloramphenicol given; rheumatoid arthritis, which had been dormant for many years, became quite severe postoperatively; triancinalone (16 mg. daily for 2 days) caused prompt improvement; 2nd course Nitromin, May 12, 1958 (15 mg. daily orally for 10 days); again no leukopenia; *6 weeks after surgery abscess on lower abdominal wall; drained, chloramphenicol again given; small fecal fistula found which later closed spontaneously; complete regression, gained 9 lbs.; by July 23, 1958, a 3 × 3 cm. nodule palpable in liver; this also disappeared; no further evidence disease*; 1962 developed persistent leukopenia (1,200-2,500 wbc), thrombocytopenia and absolute eosinophilia, frequently marked; alive and well August 1968; died heart failure 1972, (589; 812).

12 yrs.

34. (*Edland*): Male aged 3; inoperable very cellular rhabdomyosarcoma (botryoid type) of right middle ear, extending into pre- and post-auricular regions, with destruction of bone anteriorly including a portion of the zygomatic process, $4\frac{1}{2} \times 6$ cm.; *concurrent pseudomonas infection of middle ear, and mastoiditis with abscess formation*; early September 1967 surgery revealed extensive tumor, unresectable; biopsied; September 5, 1967 telecobalt (5 a week 300 R each air exposure) total 7520 rads tumor dose in 44 days; concomitant chemotherapy: actinomycin D in 5 days (i.v., 0.15 mg/kg); *continued infection*: ear drainage continued, actually increased during radiation, then decreased rapidly after completion of radiation; healing proceeded rapidly; *continued intermittent episodes of drainage from ear required intermittent antibiotic therapy for 3 yrs; extensive tumor regressed completely*; NED until August 1969, asymptomatic metastasis seen in right lower lung; X-ray (6800 rads, tumor dose); and a further brief

SERIES A, GROUP 1, DETERMINATE SUCCESSES

course of actinomycin D (5 i.v. in 5 days, 0.15 mg/kg); further courses given for about a year, alternating with vincristine; child in good health, attending school, NED 1980. (93; 227a).

13 yrs.

35. (Baker): H.L., male, aged 46; recurrent, inoperable malignant melanoma rt. ear, metastasis to lymph node in parotid region; onset, March 1955; 3 mos. later lesion burned off by local physician; recurrence in 1 mo.; incisional biopsy of 8.8 mm. recurrence, March 12, 1956; subtotal resection ear in continuity with parotidectomy, radical neck dissection, March 21, 1956; 9 mos. later recurrent nodules present; these doubled in size by March 21, 1957; large tumor mass *grossly infected* by June 1957, fungated through skin of upper cervical region, extending over mastoid onto rt. cheek, fixed to deeper structures, bled easily; patient repeatedly refused hospitalization, as he feared further surgery would affect facial nerve; patient himself resected the recurrent lesions with pocket knife and scissors, losing much blood in the process (frequent hemorrhages from the tumor); *complete regression*, leaving extensive depigmented scar, no further recurrence; serious internal injuries in auto accident February 1977, required splenectomy and replacement of stomach found in thoracic cavity; alive and well March 1980. (17a; 93).

25 yrs.

36. (McCarthy et al): J.A., male, aged 41, inoperable malignant melanoma back of rt. knee with metastases to right groin and small bowel; April 1967, small non-pigmented mole burned off posterior knee; October 1967, lump in right groin (present for 6 mos.) biopsied; wide local excision of primary site, in continuity block dissection of groin; several nodes were metastatic; *postoperative wound necrosis, loss of graft, local infection*, venous thrombosis in leg, multiple pulmonary emboli, *pleural effusion of left lung*; recovered, well 5 mos.; March 1968 increasingly severe colicky abdominal pain, nausea, emesis; continued for 4 mos., 28 pound weight loss; August 1968 exploratory laparotomy revealed intussusception of ileum from *partially necrotic* polypoid mass; 30 cm. of dilated small bowel resected, end to end anastomosis; $8.5 \times 5.2 \times 5$ cm. growth involved mucosa, submucosa and infiltrated muscularis propria; numerous other metastatic nodules throughout small intestines (pinhead to 2 cm. in size) were not touched; *post-operative fever and large wound abscess which was drained; wound healed in 3 wks.; remaining metastases regressed; during next 10 yrs. intermittent cellulitis of rt. leg*; patches of vitiligo appeared on arms and on graft on rt. leg; well, n.e.d. 1978. (478a).

11 yrs.

37. (McCarthy, et al): Mrs. E.E., female, aged 62; inoperable recurrent metastatic malignant melanoma primary in lt. lower leg, with metastases in left inguinal nodes; recurrence had infiltrated subcutis, and underlying muscles, lymphatic and vascular invasion also present; January 1970, small

SERIES A, GROUP 1, DETERMINATE SUCCESSES

melanoma excised from lt. lower leg, defect repaired by skin graft; well 5½ yrs.; August 1975 lump in lt. groin; radical lymphadenectomy; several nodes contained metastatic malignant melanoma; *postoperative fever and wound infection*; local recurrence in groin; attempted removal abandoned as lesion extended to femoral artery; in 3 mos. mass 20×8 cm. developed in region of groin scar; *1 dose BCG given, negligible reaction*; transferred to terminal care hospital; *discharged in 3 mos. as mass had regressed considerably, it had disappeared by October, 1976*, remission accompanied by neurological symptoms later regarded as due to polymyositis; alive and well August 1978. (478a).

8½ yrs.

SERIES A, GROUP 2, INDETERMINATE SUCCESSES: 54 CASES

Type of Tumor

- 22 carcinoma: #1, 2, 3, 10, 11, 13, 14, 15, 18, 22, 24, 25, 39, 41, 43, 44, 47, 48, 49, 50, 51, 54
- 16 sarcoma of soft tissues: #4, 5, 8, 17, 19, 23, 30, 31, 33, 34, 36, 38, 40, 45, 46
- 8 epithelioma: #6, 20, 26, 27, 28, 29, 35, 37
- 3 sarcoma of bone: #12, 42, 53
- 2 malignant melanoma: #9, 21
- 1 chorionepithelioma: #32
- 1 hypernephroma: #52
- 1 lymphadenoma: #16
- 1 not stated: #7

Type of Infection

- 41 streptococcal:
 - 38 erysipelas: #4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 31, 33, 35, 36, 37, 39, 40, 41, 43, 44, 45, 47, 49
 - 2 other than erysipelas: #42, 46
- 6 supuration: #1, 3, 18, 32, 38, 50
- 7 abscess and/or sepsis: #2, 11, 24, 42, 48, 51, 54
- 2 staphylococcal: #52, 53
- 1 Bacillus pyocyaneus: #42

Site of Primary Tumor

- 20 head and neck: #4, 5, 6, 19, 20, 21, 22, 23, 26, 27, 28, 29, 30, 31, 33, 34, 35, 37, 38, 45
- 14 breast: #1, 3, 8, 10, 11, 13, 14, 16, 18, 24, 25, 44, 47, 48
- 5 soft tissues: #2, 9, 17, 36, 40
- 3 bone: #12, 42, 53
- 3 uterus: #7, 15, 32
- 1 intra-abdominal: #43
- 1 ovary: #51
- 1 ectopic testis: #39
- 1 renal: #52
- 1 penis: #41
- 1 vulva: #49
- 1 anus: #50
- 1 widespread (Kaposi sarcoma): #46
- 1 colon: #54

SERIES A, GROUP 2, INDETERMINATE SUCCESSES, BRIEF ABSTRACTS (54 CASES)

These inoperable cases developed pyogenic infections spontaneously (72% were erysipelas), followed by complete regression. They are regarded as indeterminate because either the patients were traced less than five years, or the records do not indicate whether the diagnosis was confirmed histologically. However, 11 of the cases were recurrent (three being twice recurrent), and in 1 other metastases were present when infection developed. Many were published by well known, experienced surgeons of their day. Therefore we believe this group also deserves to be considered in evaluating the possible beneficial effects of concurrent pyogenic infections in inoperable cancer.

The name in parenthesis following the case number in these brief abstracts refers to the physician or hospital handling or publishing the case. Bibliography reference numbers are given at the end of each abstract. Detailed histories of most of these cases are available at the Cancer Research Institute, for those who wish to study them more thoroughly, including some of the comments of the reporting physicians.

1. (*Schwenke*): Female adult; inoperable mammary cancer, resistant to various internal medications such as hemlock; treatment stopped; abscess on leg formed; *as suppuration became more abundant, cancer diminished, then completely disappeared*; against advice, patient allowed ulcer on leg to heal; cancer at once recurred; new wound was opened at site of abscess, *when suppuration was well established, cancer again disappeared gradually*, as it had the first time. Case published in 1774, end-result unknown. (217, 583k, 851, Case 80, p. 119).

2. (*Boyer*): N.L., male, aged 52, extensive inoperable scirrhus carcinoma of back, involving trapezius and great dorsal muscles; incomplete excision; prompt local recurrence; prognosis hopeless; *attack of fever caused complete disappearance except for withered wrinkled skin*; at same time severe pulmonary symptoms developed and death seemed imminent; *an abscess then formed, respiration became freer, patient recovered completely*; in perfect health 18 months; disease is said to have recurred. End result unknown. (444, p. 27; 851, p. 208).

3. (*Dupuytren*): Female, aged 50; inoperable scirrhus carcinoma breast of 2 years duration: May 1811 "*laudable suppuration*" developed, *following exploratory incision; growth disappeared rapidly*. End-result unknown. (851; 853k; 892).

4. (*Sambin*): Male, aged 54; inoperable sarcoma left cervical region twice

Over 18
mos.

SERIES A, GROUP 2, INDETERMINATE SUCCESSES

the size of man's fist, almost immovable; potassium iodide given; ulceration; *erysipelas over neck, head, complete disappearance of growth leaving granulating wound*; remained well when last traced. (373, p. 12).

5 yrs.

5. (Busch): Female, aged 43; inoperable sarcoma of face, prominent tumor under left eye, several smaller nodules; onset, August 1863; partial excision largest growth; *severe erysipelas developed in wound, spread over head and neck; tumors became very much swollen, then softer and smaller; during second attack erysipelas nodules again became tense; lower half large growth beneath eye sloughed away; remainder began to shrink; regression especially rapid during week when patient had an attack of diarrhea; growths completely disappeared*; no recurrence when last traced, 1866. (This is the first recorded case of cancer in the medical literature, regarded as a permanent cure by Fehleisen, in which erysipelas caused regression.) (72; 87-89; 125; 243; 566; 867).

3 yrs.

6. (Lussana & Tansini): Female, aged 52; inoperable ulcerated epithelioma temporal region size of turkey egg, frequent profuse hemorrhage, of 4 years duration; 2 enlarged lymph nodes; gastric juice applied 3 times; *erysipelas developed; growth regressed 50% in 5 days; lymph node regressed completely, the other broke down, discharged necrotic tumor tissue*. Gastric juice applied a 4th time; growth opened, continued to decrease in size, reduced in 11 days to a flat, healthy granulating wound: *primary and metastases completely disappeared, general condition excellent*; well approximately 5 years after onset, 1 year after erysipelas. (72; 125; 181; 476).

5 yrs.

7. (Mosengeil): G.K., female, aged 28; inoperable intra-abdominal tumor involving left uterus and parametrium, developed immediately after confinement, increased very rapidly, hard and painful; 2 mos. after onset, June 1, 1869, *severe facial erysipelas, fever (over 40° C.) lasting 20 days. Pain and tumor entirely disappeared*; end-result not recorded. (56; 227; 560; 561).

?

8. (Mishtolt): Adult (sex not given); inoperable sarcoma left sternomastoid, 4 × 8 cm.; two parenchymatous injections chloride of zinc; *erysipelas infection of neck, shoulder, chest, lasting 12 days; complete disappearance of tumor in 6 weeks*; recurrent nodule appeared a year later; end-result not recorded. (125; 193; 306; 344; 545).

1 yr.

9. (Plenio): Female, aged 22; inoperable extensive malignant melanoma gluteal region extending to iliac spine, fold of buttock, onto abdominal wall; iliac lymph nodes enormously enlarged; removal attempted; *severe erysipelas (phlegmonous); gangrene of skin, thrombosis, septicemia; patient almost*

SERIES A, GROUP 2, INDETERMINATE SUCCESSES

died; extensive growth entirely disappeared during convalescence; no recurrence, well and free from disease when last traced. (72; 257; 260; 652; 676).

2 yrs.

10. (Esteves): J.N., male, aged 70 to 75; inoperable scirrhus cancer right breast, several well-marked areas of induration, ulcerated area 0.4 6 cm. in diameter; *erysipelas infection over right breast, thorax, shoulder; nodules swelled 1-2 cm. during infection; after infection breast completely flaccid, no induration remained.* End-result unknown. (232; 583k).

?

11. (Gluck): Female adult; extensive inoperable recurrent carcinoma left breast, involving mammary region and large portion thoracic wall, numerous skin metastases, exostosis femur, region greater trochanter, pain in tibia; *deep pyogenic abscess in affected breast; patient almost moribund; gradual recovery, all evidence disease disappeared, including femoral exostosis, skin metastases and recurrent growth; end-result unknown.* (583k, 906).

?

12. (Gerster): Male, adult, recurrent inoperable sarcoma femur; amputation at trochanter minor, recurrence in stump; prognosis grave, *very severe erysipelas beginning in stump; recurrent growth disappeared completely; no further evidence of disease; in perfect health when last traced 3 years later.* (126; 316, discussion by Gerster).

3 yrs.

13. (Franceschi): G.T., female, aged 61; recurrent ulcerated inoperable carcinoma right breast; recurrent following mastectomy; *erysipelas infection caused complete disappearance; ulcerated area healed rapidly by healthy granulation; end-result unknown.* (265; 583a).

Over 6
yrs.

14. (Mohrs): Mrs. E.M.H., age 83, inoperable ulcerated carcinoma left breast, multiple metastases in axilla, supraclavicular region and skin surrounding primary growth; pronounced cachexia, intense pains; conium, later belladonna given also "earth dressings to absorb discharge"; bedridden; *severe erysipelas extended from affected breast to neck and ilium; high fever; arsenic given; rapid disappearance metastases, primary growth regressed, ulcerated area drier, less offensive; all evidence of malignant growth disappeared, also cachexia; gained weight; fell out of bed fracturing humerus 4 months later; bone healed very rapidly, no disability.* (549; 583a).

3 yrs.

15. (Bidlot): Female, aged 40; inoperable far advanced cancer uterus; cachectic, bedridden several months; *severe erysipelas (almost fatal); all symptoms uterine cancer gradually diminished; well 2 years; all former symptoms recurred, condition again serious; inoculation of erysipelas considered; severe bronchitis; croton oil rubbed on chest caused violent erysipelas over*

SERIES A, GROUP 2, INDETERMINATE SUCCESSES

whole trunk, thigh; again complete disappearance uterine cancer. No further recurrence, symptom free. (39; 515; 519; 583j). 11 yrs.

16. (Kleeblatt): E.K., female, aged 21; inoperable lymphadenoma beneath left eye, of very rapid growth, size of pigeon egg; iodide of potassium salve applied; *erysipelas infection followed; tumor ulcerated, discharged necrotic tumor tissue*; after several days ointment again applied and *2nd erysipelas infection occurred; tumor disappeared completely*; recurrence did not take place; remained well. (56; 125; 193; 216; 345; 383; 566; 719). 2 yrs.

17. (Senger): Female, aged 65; inoperable sarcoma shoulder, recurrent after shoulder amputation, mass size adult head, invading anterior chest; methyl violet injected 10 times; *erysipelas then developed in tumor area, growth softened*; incised, degenerated tissue evacuated; *complete disappearance*; no further recurrence; alive and well. (664). 6 yrs.

18. (Perrin): Female, aged 64; inoperable cancer breast, with axillary metastases also enormous goitre; cancer untreated, goitre operated; *breast cancer then became inflamed, suppurated; completely disappeared*, leaving depressed scar; not traced. (583k; 662; 931). ?

19. (Sell): Male, aged 18 months; inoperable very extensive sarcoma right inframaxillary region and throat (congenital); inoperable at 8 weeks; increased in 16 months to size of child's head, pushing esophagus and trachea to one side, causing much dyspnea and difficulty in swallowing; child emaciated, general condition poor; *facial erysipelas, fluctuation in 5 or 6 areas; discharge necrotic lumps, suppuration for 6 months; complete regression; respiration, deglutition normal; gained weight and strength*; developed in similar fashion to siblings; remained well and free from recurrence. (778). 4 yrs.

20. (Collins): Mr. M., male adult; inoperable epithelioma-right cheek, 4 × 2½ cm., ulcerated for 10 yrs., granulations soft, bled at touch, painful; *facial erysipelas, extending from nose to nape of neck; ulcer looked healthier, healed in 2 weeks, normal appearance*; 3½ months later, smooth firm cicatrix. (154). Over 10 yrs.

21. (Northrop): Mrs. F., female, aged 80; inoperable 3 times recurrent malignant melanoma, primary in nasal cavity, metastases in sternomastoid muscle; extensive infiltration, severe pain; *facial erysipelas; 9 days later metastatic mass considerably smaller, more movable, pain entirely gone; general condition greatly improved; in another 10 days all evidence of disease disappeared*; 4 months later further recurrence; 3 tumors removed from

SERIES A, GROUP 2, INDETERMINATE SUCCESSES

sheath of common carotid, another from inner side right cheek; wounds healed well; not heard from again. (257; 596; 597; 898)

?

22. (Smith): Mrs. C., female, aged 88; inoperable ulcerated cancer covering $\frac{1}{4}$ of nose, malar region; indurated area surrounded ulceration, infiltrating naris; *simultaneously erysipelas developed on one limb and on face, high fever, chills; spread rapidly; ulcerations became very inflamed, swollen, then shrivelled and changed; hydrogen peroxide and very hot water applied locally; general tonics (including iron and nux vomica); complete disappearance; no recurrence, died other causes at 89. (799).*

Over
16 mos.

Mazzoni (1894) described a case of extensive uterine carcinoma which was completely cured by an erysipelas infection. Since no details were given the case is not included in the statistics. (524; 776).

23. (Billroth): Age and sex not given; inoperable sarcoma pharynx; *severe facial erysipelas; tumor mass sloughed, large defect healed rapidly by granulation leaving healthy scar at site of former growth; considered cured. (178; 781).*

?

24. (Schuler): Female adult; inoperable mammary carcinoma; *extensive abscesses in region of tumor; 125 cc. pus evacuated; fever for 18 days; complete regression; gained seven kilos; later recurrence; end-result unknown. (344; 583k; 769).*

?

25. (Boomer): Female, adult; very extensive carcinoma breast involving 60 square inches; patient entered hospital to die about 1895; developed *violent attack erysipelas; growth completely disappeared in 6 wks.; no recurrence or metastases; alive and well 1904. (137, p. 210; 583k).*

9

26. (Neale): Male adult; epithelioma on nose of 8 years duration; *severe facial erysipelas extending over entire head; growth completely disappeared; no recurrence; alive and well thereafter. (138, Case VI in Table, Accidental Erysipelas).*

Over
5 yrs.

27. (Pacinotti): T.F., female, aged 78, ulcerated inoperable epithelioma lip, large metastases submaxillary lymph nodes; cachectic; *severe facial erysipelas beginning on ulcerated tumor, fever to 40°C.; striking fluctuation in metastatic nodes apparent by 4th day; incision, necrotic tumor tissue evacuated; primary and metastatic growths disappeared completely; gained weight, strength, in perfect health thereafter. (188; 344, Case 27, Table 3, p. 544; 621).*

5 yrs.

SERIES A, GROUP 2, INDETERMINATE SUCCESSES

28. (*Matas*): Age and sex not given; inoperable epithelioma of ear, involving parotid; incomplete surgical removal; recurrence regarded as inevitable; *severe erysipelas during wound healing; remains of growth disappeared, no recurrence*, alive and well when last traced. (123; 137, Case VII). 5 yrs.
29. (*Boomer*): Adult male, inoperable epithelioma face of 18 years duration (in scar of old burn); condition considered hopeless; *erysipelas; growth entirely disappeared immediately afterwards*; local recurrence several years later; Coley toxins then given for 2 months; ulcerated growth healed in first 4 weeks; another local recurrence 6 months later; alive over 20 yrs after onset. (137, Case III, p. 210). 20 yrs.
30. (*O'Keef*): Mrs. H., female, aged 35; twice recurrent inoperable very extensive multiple sarcoma of neck, involving right breast, axillary, cervical nodes, mastoid to clavicle; cervical growth dissected in 2 hours, patient's condition poor, so egg-size tumor of breast and axillary growths untouched; *erysipelas over whole back, arms, chest; high fever (102°-105° F. for 6 weeks) 3 more attacks; diminution in breast tumor noted on 10th day, nothing remained but small dimple when eruption subsided; axillary nodes also disappeared*. Well and free from recurrence. (608). 1 yr.
31. (*Meriwether*): Age and sex not given; inoperable sarcoma parotid and jaw; *facial erysipelas; complete disappearance*; later metastases in tibia; Coley toxins given "with success" end-result unknown. (536). ?
32. (*Hörmann*): Female, aged 36; inoperable chorioepithelioma uterine body; following spontaneous abortion; September 15, 1900; vaginal metastases, (confirmed microscopically); constant hemorrhages; pain; uterus firmly fixed, nodular in outline; exploratory operation; masses curetted from greatly enlarged uterine cavity; thereafter dry cough, cramps, dyspnea, some bloody sputum indicating pulmonary metastases; rapid cachexia; bedridden; another metastatic nodule on introitus excised; April 30, 1901: *severe postoperative infection, fever to 41° C., repeated chills*; another curettage few days later. *Fever continued for weeks; complete disappearance all involvement uterus, cervix, lungs*; normal pregnancy, confinement, child healthy; *no further recurrence or metastases*, uterus size hen's egg 1903, 2 years after infection, almost 3 years after onset. (174; 282; 340; 344; 583j). Almost 3 yrs.
33. (*Johnston*): Male adult; recurrent round cell sarcoma cervical lymph nodes; primary growth beneath chin excised; recurrence in both cervical regions within a few weeks; all affected nodes dissected from one side of neck, upper chest; *violent erysipelas over neck, upper chest; all the affected*

SERIES A, GROUP 2, INDETERMINATE SUCCESSES

nodes on other side of neck disappeared completely; end-result unknown. (917).

?

34. (*Marchetti*): Male, aged 56; inoperable twice recurrent small round cell sarcoma suprahyoid region; primary growth size hen's egg excised 5 months after onset; rapid local recurrence; more extensive 2nd operation; again recurrence of rapid growth involving entire suprahyoid region; went home against advice; tumor very much larger, rather hard, fleshy consistency; patient gravely prostrated; then developed *severe erysipelas lasting 8 days beginning in tumor area involving whole face, high fever, patient delirious, hard tumor decreased in size, sinus area dry; regression continued; complete in 4 weeks, gained weight, strength, resumed work, skin soft, smooth, good scar.* No further recurrence. (503).

1 yr.

35. (*Copeland*): Sex not given, aged 85; extensive epithelioma face, cheek, eye, nose; *completely disappeared following attack of erysipelas; died unrelated causes, no evidence recurrence or metastases, 2 years later.* (137, p. 210).

Over 2
yrs.

36. (*Senn*): Age and sex not given; untreated inoperable sarcoma fascia between scapulae; *growth became infected with erysipelas, disappeared completely; end-result unknown.* (137, p. 219).

?

37. (*Rixford*): Female, aged 73, extensive epithelioma face and neck, recurrent following radical removal; *erysipelas lasting 2-3 weeks (of moderate severity); tumor became very much smaller, finally entirely disappeared; recurrence deep in base of neck 4 months later; very extensive operation, enormous flap thrown up from chest; excellent result; no further recurrence; end-result unknown.* (708).

?

Kappes reported a case of epithelioma of the forehead in which a concurrent erysipelas caused "complete healing." As no details were given, the case is not included in the statistics. (344; 373).

38. (*McMaster*): Mr. C., male, aged 67; inoperable round cell sarcoma neck at angle of jaw extending from mastoid to clavicle; very rapid growth, very hard, jaw fixed; x-ray for 4 months; Coley toxins given during 3rd month, no immediate effect noted; tonics also given; *growth melted away rapidly, following suppuration (first in upper, then in lower part of growth; slight toxemia; gained weight, strength after suppuration ceased; growth disappeared, no further recurrence, alive and well.* (486)

1 yr.

39. (*Bolognino*): Male, aged 47; recurrent, extensive adenocarcinoma ec-

SERIES A, GROUP 2, INDETERMINATE SUCCESSES

topic testis; incomplete removal of recurrence; 2 severe *erysipelas* infections in region of wound; remains of growth regressed; no further recurrence or metastases. (56; 344, Case 29, Table 3).

4½ yrs.

40. (*Bolognino*): Age and sex not given; recurrent round cell sarcoma axilla; primary growth removed; recurrence incompletely curetted; very severe *erysipelas* infection; remains of growth completely disappeared; no further recurrence when last seen 13 months later; end-result unknown. (56: 716, p. 206).

Over 18
mos.

41. (*Odier*): Adult male; inoperable cancer penis; *erysipelas*; complete regression; well and free from disease 7 years, recurrence then developed; end-result unknown. (344, p. 542).

7 yrs.

42. (*Rotgans*): Female, aged 65; inoperable osteosarcoma of sternum, formless nodular bony mass, size of child's head when first seen, involving most of the sternum, extending over 4 or 5 ribs to left, mostly to right, base 20 cm., height 8 cm. in diameter; condition regarded as incurable so was not admitted; lost to view 10 months; nodular growth had increased to size of man's head, discharged large quantity of bloody material from ulcerated area size of man's palm; growth involved ½ of chest wall; September 1912: tumor became infected (*Streptococcus longus* and *Bacillus pyocyaneus*); handfuls of necrotic hemorrhagic tumor tissue sloughed out, wound became clear: "miraculous outcome," complete disappearance in 33 days; chest flat; x-ray examination showed no further tumor shadow, only a thick misshapen spongy sternum; tumor recurred under left pectoralis major muscle; at operation it extended into thoracic cavity involving cartilages; portions of 2 ribs resected; closed abscess found containing thick pus; wound healed but temperature remained high, further postoperative infection, various abscesses extended from intrathoracic cavity behind ribs near sternum into lower intercostal space, also in abdominal wall; as they developed they were incised; pus, degenerated bony sequestrae were evacuated; whole sternum divided, space beneath cleaned of remaining bony sequestrae; recovery 1 month later; further recurrence developed on both sides of incision in sternum; injections of pus obtained from abscesses, no effect; recurrence excised; new abscesses found; after 8 months' hospitalization tumor and abscesses were "conquered," patient looked well, had regained strength and wished to be discharged; case then published, end-result unknown. Detailed history of this unusual case deserves study. (733).

Over 1 yr.

43. (*Strandgaard*): Mr. S., male, aged 75, enormous inoperable intra-abdominal carcinoma, apparently originating in colon, involving small, large intestines, omentum, adherent to prostate, bladder and bony pelvis

SERIES A, GROUP 2, INDETERMINATE SUCCESSES

with subcutaneous metastases in abdominal wall; patient emaciated with very painful tenesmus; laparotomy revealed ascites; lateral colostomy (diseased portions of appendix epiploica pulled out); these increased in size enormously in 4 days; 10 days later *severe erysipelas involving whole body, beginning in lumbar region; very ill, high fever; tumor mass in colostomy wound, large abdominal tumor, subcutaneous metastases all disappeared; soon had normal defecation through rectum, felt quite well*; allowed home in 5 weeks; few months later developed acute nephritis, causing death; no autopsy. (258, 838, Case 1).

About 1
yr.

44. (*Strandgaard*): S.K.G., female, aged 59; twice recurrent inoperable adenocarcinoma breast, suspected pulmonary metastases; radical mastectomy 16 months prior to infection; weak heart and bronchial symptoms prevented further surgery; some x-ray treatments given; 2 weeks later *severe erysipelas, recurrent nodules disappeared, scars absolutely smooth; no evidence of disease thereafter*; died 9 days after last examination of myocarditis, bronchopneumonia, 11 years after onset, 6 months after regression following erysipelas. (583k; 589; 838).

11 yrs.

45. (*Wolfheim*): Male, aged 62; inoperable round cell sarcoma nasopharynx, involving inferior maxilla and throat; *developed erysipelas; within 3 weeks complete regression of tumors occurred*; end-result not recorded. (345; 356, Case 26 in Table 2).

?

46. (*Goodwin*): Male adult; Kaposi's sarcoma cervical lymph nodes, involving skin; 1 node excised from neck, shortly thereafter numerous metastatic lesions appeared in skin; some regressed under x-ray therapy but new ones appeared, general condition gradually declined; *streptococcal infection on knee; striking general improvement, new metastatic nodules appeared with less frequency, finally all remaining nodules disappeared completely*; patient not traced subsequently. (123; 589).

?

47. (*Kilroe*): Female, aged about 50; inoperable carcinoma left breast, Grade IV, axillary metastases, left arm edematous; simple mastectomy, no attempt to remove axillary metastases; *2 or 3 days later severe, almost fatal, erysipelas, temperature 103°-104° F., lasted 6 weeks, several transfusions given; complete regression axillary involvement; no further edema of arm*; well, free from disease. (583k; 589).

Over 1 yr.

48. (*Wintz*): Age and sex not given; inoperable recurrent mammary carcinoma with metastases; *sepsis with abscesses; complete regression recurrent and metastatic masses*; no further evidence of disease. (344, p. 543, Case 7).

10 yrs.

SERIES A, GROUP 2, INDETERMINATE SUCCESSES

49. (W.B. Coley): F.J., aged 73, inoperable very extensive carcinoma vulva, involving both labia, extending well up vagina; radium applied in form of dental mold; 12 days later *severe facial erysipelas lasting 10 days, during which tumor showed a striking change, becoming rapidly smaller; complete disappearance in 3 weeks*; growth replaced by healthy granulation tissue which healed over with normal epithelium in a few weeks; no recurrence or metastases; died at age of 82 following fall which fractured femur. (123; 528; 583j; 589).

9 yrs.

50. (Gregoire): Male adult; terminal pavement cell carcinoma anus, invading perineum from ischium to ischium, region of bulb of ureter almost to coccyx with rectal fistulae; *suppuration; electrocautery used*; patient relieved of suppurating fistulae and tumors; *alive and in good condition thereafter*. (298).

Over
4 yrs.

51. (Levine): Young female adult; enormous inoperable adenocarcinoma ovary arising during pregnancy; abdomen very distended, labor induced prematurely; abdomen continued to increase rapidly in size postpartum; exploratory laparotomy revealed very extensive inoperable growth extending up to and attached to spleen and stomach; some of it removed (tumor ruptured during operation); condition hopeless; no radiation given; *severe sepsis postoperatively, lasting several weeks, abscess evacuated; complete regression, no evidence of disease*; alive and well thereafter. (589).

Over
4 yrs.

Janker cited Muller's case of inoperable enchondroma of lower abdomen and hip in a male, aged 43. Following attempted surgical removal, *regression occurred "due to suppuration."* No further details given, so the case is not included in the statistics. (356).

52. (Buehler, Bettaglio & Kavan): Male, aged about 59; hypernephroma of left kidney, with extension to caval and aortic areas, involvement of renal vein and bilateral pulmonary metastases; onset, urinary frequency, dysuria, 1954; i.v. pyelogram showed kidney was tilted; 1956, 1958, had several bouts of gross, total painless hematuria the last in late September 1958; 5 lb. weight loss in 2-3 years; although disease was extensive and metastases were present; nephrectomy was performed, November 19, 1958; tumor mass 15 × 30 cm. was removed; *post-operative staphylococcal infection; gained 20 lbs. in next 10 months, symptom free, pulmonary metastases had almost completely disappeared by September 1959*; inguinal herniorrhaphy then done; *again had post-operative staphylococcal infection which cleared very slowly; no further evidence of disease* when last traced, 3½ years after first hematuria and 5 years after onset of urinary frequency and dysuria. Lost to follow-up thereafter. (75; 589).

5 yrs.

SERIES A, GROUP 2, INDETERMINATE SUCCESSES

53. (*Jakoubkova, et al*): J.V., male, aged 60; malignant osteogenic sarcoma of right ulna; with bilateral pulmonary metastases; onset 1962, weakness, easy fatigueability of arm; January 1964, pain, swelling apparent on dorsal right forearm; explored February 1964; *postoperative phlegmona, drainage antibiotics*; disease progressed rapidly; amputation advised, refused; again explored; pathologist reported malignant transformation; March 26-May 12, 1964: x-ray (4,000 r tumor dose); disease progressed, lung metastases apparent 2 weeks after completing radiation; *fever, necrosis of soft parts, fistula, Staphylococcus epidermidis, pyogenes and Achrobacterium*; chloramphenicol, neomycin and erythromycin given; temporary effect only; *again became febrile; lung metastases regressed slightly during further infection*; amputation finally performed June 22, 1964; rapid improvement in general health; *lung metastases at first increased, then disappeared* by November 1964, 5 months after amputation; in excellent health until sudden death, October 13, 1966, myocardial infarction. (354).

4½ yrs.

54. (*Vietta*): Male, adult, inoperable colon carcinoma, causing obstruction; lesion resected; bone scans a yr. later showed rapidly growing metastases in lung; very rapid down hill course, with ascites; prognosis regarded as 2 weeks; developed tender area in right leg, *huge subphrenic abscess developed involving whole right flank to pelvis; with fever*; incision and drainage; tiny ventral hernia corrected, no evidence of disease seen; traced well 18 months later. (93).

2 yrs.

SERIES A, GROUP 3, INCOMPLETE REGRESSIONS: 19 CASES

Type of Tumor:

- 8 carcinoma: #1, 7, 9, 11, 12, 13, 14, 15.
- 5 sarcoma of soft tissues: #8, 10, 16, 17, 19.
- 3 epithelioma: #2, 3, 5.
- 1 sarcoma of bone: #6.
- 1 malignant melanoma: #18.
- 1 type not recorded: #4.

Type of Infection:

- 17 erysipelas: #2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19.
- 2 suppuration: #1, 15.
- 1 abscess: #13.

Site of Primary Tumor:

- 9 head and neck: #2, 3, 5, 6, 9, 10, 13, 16, 17.
- 6 breast: #1, 4, 7, 11, 12, 14.
- 3 sarcoma of soft tissues: #8, 18, 19.
- 1 gall bladder: #15.

SERIES A, GROUP 3, INCOMPLETE REGRESSIONS: BRIEF ABSTRACTS, (19 CASES)

These 19 inoperable cases developed pyogenic infections spontaneously followed by incomplete regression, the end-result being unknown. The names in parentheses following the case numbers refer to the physician or hospital handling or publishing the case. The abstracts are listed chronologically. At the end of each abstract bibliography reference numbers are given. Detailed histories of 60% of these cases are available.

1. (*Martinet*): Female, aged 66; very advanced inoperable mammary carcinoma, metastases to axillary and clavicular lymph nodes; growth extended from axilla to sternum, clavicle to costal margin; extreme cachexia; compresses applied without apparent benefit; she then developed severe throbbing in tumor, great malaise (no fever); *abundant suppuration; marked decrease in size of neoplasm, increase in mobility, pains ceased*; compresses applied, best possible diet prescribed; *strength, appetite returned, very marked regression; as suppuration diminished, nodules increased; further suppuration, growth later regressed to size of goose egg, all but 3 of 13 sinuses healed through which necrotic tumor had drained*; end-result unknown. (510; 583k; 851, Case 70, pp. 102-106).

2. (*Bardeleben & Völker*): Female, aged 54; inoperable epithelioma inner canthus right eye, involving eyeball (*cornea perforated*) of 2 years duration; 4 attacks erysipelas, none severe (each successive one milder); *lens discharged through corneal perforation, also pus, necrotic tissue; pains ceased, general health improved after first attack*; later tumor began to grow toward left eye; pain returned; silver nitrate and saline injected into tumor twice (Thiersch's method) caused edema, severe pain, cessation growth, *tumor softened, suppurated* following each injection; end-result unknown. (901).

3. (*Mosengeil*): Female, aged 50; recurrent inoperable epithelioma of cheek, nose, eyelid; large ulcerated growth, excision, rapid recurrence; actual cautery; *slight erysipelas infection lasting 2 days; growth stopped, healthy granulations formed, improvement in sight of left eye*. End-result unknown. (56; 125; 193; 306; 560; 561; 566, p. 33).

4. (*Stein*): Female, aged 48; extensive, inoperable, hard, nodular tumor right breast; skin adherent, veins dilated, growth fixed to chest wall, cachexia; injection pyrophosphate of iron and citrate of soda given for anemia; *erysipelas developed 12 hours later at site of injection; spread over neck, chest, head, lasting 12 days; growth disappeared except for 2 small indurated nodules, great improvement in general health*; end-result unknown. (72, p. 449; 125, Case 8 in Table; 566, p. 31; 583k; 824).

5. (*Esteves*): F.B., male, aged 60; ulcerated inoperable epithelioma cheek, lip, right side of nose, extending to external canthus of eye, invading mouth internally; *erysipelas infection of whole median zone of cheek with great edema of eyelids on left side, abscess*

SERIES A, GROUP 3, INCOMPLETE REGRESSIONS

of left lower lid; partial regression of external part of growth, no effect on portion in mouth. End-result unknown. (232).

6. (*Powers & Dowd*): Female, aged 52; inoperable sarcoma superior maxilla; *growth regressed 50% within 2 weeks after erysipelas infection. Recurrence; end-result unknown. (125, Case 29 in Table; 344).*

7. (*Morris*): Female, aged 26, recurrent inoperable carcinoma breast; *erysipelas infection lasting 10 days; marked decrease in size; end-result unknown. (123; 125; 583k).*

8. (*Powers*): Female, aged 32; recurrent round cell sarcoma foot, extensive, ulcerated metastases in thigh and pelvis; *mild erysipelas infection; slight temporary improvement; thereafter growth rapidly increased in size; end-result unknown. Two early weak preparations of Coley toxins, (Types III and IV) were also given in this case causing retardation growth rate from Type IV, no effect from Type III. (125; 126).*

9. (*Dandridge*): Male, aged 63; inoperable carcinoma neck; $8 \times 10 \times 8$ cm. in diameter; *erysipelas infection lasting 10 days, during which growth regressed 50%; remained stationary a while, then again began to increase; end-result unknown. (127).*

10. (*Dandridge*): Age and sex not given; sarcoma neck, patient given injections anhydrous sulphate of zinc; *violent erysipelas infection; growth regressed $\frac{1}{3}$, necrosis, sloughing; inhibitory effects only temporary; end-result unknown. (127).*

11. (*Coley*): Female, aged 38; advanced ulcerated mammary carcinoma ("cancer en cuirasse,") *3 severe attacks erysipelas in 3 months; slight breaking down of a few nodules, rapid healing of ulcerated areas, but no decided check on progress of disease; end-result unknown. (127; 583k).*

12. (*Westbrook*): Female, aged 43; twice recurrent inoperable scirrhus carcinoma breast, metastases in axilla, cervical nodes, ulcerated; *mild erysipelas infection over breast, axilla, arm; during first 2 days fungating growth freely broke down and discharged; by 3rd day area was "very dry, quite cleaned out, painless;" effect lasted 3 weeks; end-result unknown. (123; 127, Case 7 in Table of erysipelas cases).*

13. (*Emmerich*): Age and sex not stated; inoperable carcinoma tongue, metastases; *facial erysipelas with abscess formation; rapid though incomplete regression end-result unknown. (344, p. 544, Case 25 in Table 3).*

14. (*Koch & Petruschky*): Female adult; inoperable recurrent mammary carcinoma; *erysipelas caused arrest of growth; nodes flattened; end-result unknown. (344, Case 26, Table 3, p. 544; 391; 583k).*

SERIES A, GROUP 3, INCOMPLETE REGRESSIONS

15. (*Proescher*): A.D., male, aged 22; inoperable carcinoma gall-bladder; (typhoid fever 1896); onset, February 1906, episodes pain in epigastrium, indigestion for 3-4 hours, also constipation, jaundice; mass in epigastrium; exploratory operation May 1906; gallbladder size of orange, adherent to abdominal wall, very friable, *filled with pus*; partial excision; pathologic examination *showed very few mitoses, much colloid degeneration and fatty degeneration*; no evidence metastases seen; postoperative course uneventful although greater part of diseased gallbladder was left, no evidence recurrence or metastases; small fistula remained; second operation 13 weeks later: *gallbladder had decreased from size of orange to five cm., had become operable*; cholecystectomy then performed; *remains of gallbladder of fibrous consistency, superficially appeared very red, some normal and necrotic carcinoma cells remained*; *Proescher believed remains of growth would have disappeared had operation been deferred*. Detailed histologic findings given; end-result unknown. (689).

Huth (1952) stated that Rovsing had reported two cases of inoperable sarcoma in which there was marked regression. As no details were given these cases were excluded from the statistics. (344).

16. (*Brauth*): J.F.D., male, aged 59; recurrent round cell sarcoma superior maxillary region; growth removed with antrum of Highmore; recurrence; x-ray and radium used; marked exophthalmos; eye enucleated with part of recurrent tumor; more radium applied; recurrent growth 4 cm. in diameter; *then developed facial erysipelas; tumor almost completely disappeared, "shrivelled down to small vestige."* End-result unknown. (123).

17. (*Tage-Hansen*): Age, sex not recorded; extensive lymphosarcoma of neck; *erysipelas caused extraordinary regression of large growth*; after infection subsided tumor again began to grow; end-result unknown. (838).

18. (*Müller*): Male adult; many times recurrent, infiltrating inoperable malignant melanoma left inguinal region, multiple metastases to abdomen, left upper thigh, confirmed microscopically; recurrence involved bilateral inguinal lymph nodes; at final operation mass size of 2 fists pressed on iliac vessels causing edema left lower extremity; incomplete removal leaving platform of rough melanotic tissue size of two palms, also many egg-sized melanotic metastases in left abdomen, upper thigh and right inguinal region; *very extensive erysipelas infection then developed lasting 8 days; egg-sized nodes became nut-sized and more movable, smaller nodes disappeared entirely, quantities of melanin secreted in urine*; later tumors again began to increase in size; *another erysipelas infection developed a month later; metastatic nodes again regressed*; end-result unknown. (257; 568).

SERIES A, GROUP 3, INCOMPLETE REGRESSIONS

19. (Roussy): Age and sex not given; inoperable ulcerating sarcoma of buttocks, numerous cutaneous metastases surrounding primary growth; *erysipelas infection caused almost all nodules to disappear, primary to regress considerably*; improvement only temporary; end-result unknown. (727).

SERIES A, GROUP 4, FAILURES: 53 CASES

Of these 53 inoperable or terminal cases in whom concurrent pyogenic infections developed spontaneously, seven died of their infections (Cases 1,6,8,9,12,24,49), one died of another primary and its metastases, the original lesions having remained quiescent for five years after the infection. The other 45 cases died of their cancers.

Despite the fact that many were far advanced or terminal, very dramatic, rapid and complete regression occurred in 13, almost complete regression occurred in 9, marked regression or remission of symptoms in 13 and slight regression in 6 patients. In the other 13 cases no appreciable benefit was apparent as a result of infection. Among the seven patients who succumbed to their infections, the neoplasm had entirely disappeared in three (Cases 1,6,9) although death occurred four to nine days after erysipelas developed. It is probable that absorption of such large quantities of necrotic tumor tissue overwhelmed the reticuloendothelial system in these patients. As to the other 17 cases in which complete or almost complete regression occurred, it is significant that in most of these patients the infections were brief attacks of erysipelas, in some only mild, with little fever. Recent studies suggest that in order to control inoperable cancer more sustained administration of bacterial toxins is necessary, especially in dealing with the more differentiated or slow growing tumors. Among the 13 cases that failed to show any benefit following infection, eight were treated by Waldapfel. Most of them were far advanced and cachectic, many had had a good deal of irradiation and in several the infection was rather mild erysipelas. Of the other five in whom no benefit was noted case 12 died on the third day of an erysipelas infection; case 21 had suppuration briefly; case 26 had a mild postoperative infection; case 41 had gas gangrene; case 51 had *Salmonella montevideo*. As might be expected there were more older cases among the failures than the successes, since host responses are less easily stimulated in the older age group.

Type of Tumor:

- 21 carcinoma: #2, 6, 10, 13, 15, 16, 19, 24, 29, 31, 33, 34, 37, 39, 40, 42, 43, 47, 48, 51, 52
- 11 lymphosarcoma: #1, 7, 8, 11, 12, 17, 18, 22, 23, 38, 49,
- 6 sarcoma of soft tissues: #21, 26, 28, 30, 32, 35
- 4 epithelioma or cylindroma: #4, 14, 25, 27
- 3 sarcoma of bone: #9, 20, 44
- 1 multiple myeloma: #45
- 1 synovioma: #41
- 2 hypernephroma: #50, 53
- 1 malignant melanoma: #46
- 3 type not recorded: #3, 5, 36

Type of Infection:

- 36 streptococcal

SERIES A, GROUP 4, FAILURES

- 34 erysipelas: #1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 17, 19, 23, 24, 25, 27, 28, 29, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 42, 45
- 1 non-hemolytic strep (sepsis): #30
- 1 severe strep throat: #43
- 6 abscess: #14, 18, 20, 22, 44, 52
- 4 wound infection: #26, 46, 47, 53
- 2 suppuration: #16, 21
- 2 staphylococcal: #30, 50
- 2 pyelonephritis: #48, 50
- 1 puerperal fever: #47
- 1 pleurisy and empyema: #18
- 1 Clostridium welchii: #41
- 1 diphtheria: #40
- 1 Pseudomonas aeruginosa: #49
- 1 Salmonella montevideo: #51
- 1 type not recorded: #46

Sites of Primary Tumor:

- 25 head and neck
- 23 soft tissues: #1, 3, 4, 7, 8, 11, 12, 16, 17, 18, 22, 25, 27, 28, 31, 32, 33, 34, 35, 36, 37, 38, 39
- 2 skull: #9, 20
- 8 breast: #5, 6, 13, 15, 19, 24, 42, 48
- 4 soft tissues of foot, thigh, inguinal region: #2, 21, 26, 46
- 3 colon and rectum: #29, 43, 52
- 2 stomach: #14, 40
- 2 kidney: #30, 50
- 2 bone or synovial: #41, 44
- 1 pancreas: #47
- 1 penis: #10
- 4 primary unknown, metastatic or generalized: #23, 45, 49, 51

SERIES A, GROUP 4, FAILURES, BRIEF ABSTRACTS

The name in parentheses following the case number refers to the physician or hospital handling or reporting the case. The abstracts are listed chronologically. At the end of each abstract bibliography reference numbers are given. Detailed histories are available at the Cancer Research Institute.

1. (*Busch*): Female, aged 28; very malignant lymphosarcoma of left cervical region, size of child's head; great pain, dyspnea; deglutition almost impossible; *erysipelas*; immediate improvement, mass decreased 50% in a week, right cervical lymph nodes entirely disappeared; 9 days after *erysipelas* developed patient collapsed and died; postmortem showed growth in left cervical region had regressed to size of apple, structure reduced to network of connective tissue containing quantities of yellowish fluid; tumor cells had undergone fatty degeneration. By injecting water into growth it filled to former size. (72; 87-89; 126; 242; 244; 245; 566; 583).

2. (*Völker*): P.S., male, aged 49; extensively inoperable carcinoma inguinal region, 13 × 14 cm. in diameter, extending deeply from thigh to spine of ilium, center ulcerated, foul discharge; tumor injected by Thiersch's method (silver nitrate and saline), 1 year after onset; *erysipelas* developed in tumor area, spread over back and thigh to knee, high fever; tumor became necrotic, large portions sloughed through sinus or were removed by forceps; pneumonia then developed, conditions grave: "entire great tumor mass disappeared without leaving a trace . . . red normal muscle seen at base of wound." Death 13 months after onset. (539, pp. 343, 363-368; 901).

3. (*Nelaton*): Female, age not recorded; large inoperable encephaloid tumor of submaxillary region; *facial erysipelas* caused complete disappearance; growth recurred later, causing death. (72, p. 449; 136; 585, p. 612; 627; 894).

4. (*Pamard*): M.L., male adult; epithelioma of tongue, extensive inoperable metastases in left submaxillary lymph nodes; primary excised, tumor size of fist remained, patient barely able to open mouth, could not chew, could barely swallow; ulcerated growth, constant thick discharge; *erysipelas* over head, face, anterior thorax, lasting 10 days; most of tumor disappeared during infection; profuse salivation subsided, could open mouth, chew, swallow; within a few days growth again increased in size, disease progressed, despite papain injections; death over 18 months after onset. (72, p. 449; 125, Case 10 in Table; 566; 627; 895, p. 219).

5. (*Pamard & Delens*): Female adult; enormous encephaloid tumor of breast; *erysipelas* caused complete disappearance in 15 days, leaving wound 5 × 6 cm. in diameter which seemed to be healing; growth recurred causing death. (72, 125, Case 11 in Table; 566; 627, p. 303; 895, p. 219).

SERIES A, GROUP 4, FAILURES

6. (*Neelsen*): Female, aged 41; bilateral mammary carcinoma with axillary involvement; growth in left breast size of fist, indurated infiltrating area in right breast; left mastectomy, wound allowed to granulate; 4 weeks after surgery February 17, 1884: *erysipelas developed in wound, very severe attack, pleurisy, dyspnea; tumor in right breast diminished in size somewhat, overlying skin became gangrenous*; March 25, 1884: *2nd attack erysipelas* caused death on 10th day. *Post-mortem showed many portions of growth had undergone fatty degeneration.* (72, p. 463; 125, Case 16 in Table); 566, p. 32; 583k; 584).

7. (*Richochon*): Mme. P., aged 52; inoperable lymphosarcoma of tonsil, pharynx, with very extensive involvement cervical nodes, also those in groin; within 9 months after onset respiration, deglutition seriously affected; *facial erysipelas, fever to 40° C.; regression immediately apparent, tumors almost disappeared*; family considered patient cured; recurrence 3 weeks later; sudden death due to brain involvement. (72; 566; 583; 702; 727; 895).

8. (*Verneuil*): Young male adult; extensive lymphosarcoma of neck, respiration seriously limited by pressure of growth; lymph nodes in other regions less markedly enlarged; irritating ointment applied to neck producing excoriation; *severe erysipelas, causing death on 4th day; tumor had almost disappeared by 3rd day.* (895).

9. (*Verneuil*): Male adult; inoperable ulcerated osteosarcoma of inferior maxilla, involving submaxillary lymph nodes, floor of mouth; enormous growth, size of two fists, untreated; *severe erysipelas infection, causing death on 4th day; tumor disappeared during infection.* (246; 895).

10. (*Bardeleben & Weichel*): Male, aged 58; twice recurrent, inoperable carcinoma of penis, involving inguinal lymph nodes; *erysipelas infection of scrotum lasting 3 weeks; carcinomatous masses almost entirely disappeared*; died 2 months later, sudden hemorrhage from sinus of old surgical wound; post-mortem showed organs were normal, but carcinomatous tissue infiltrated in depth of wound. (125, Case 23 in Table; 344, p. 543; 918).

11. (*Kleeblatt*): C. F., male, aged 54; extensive recurrent lymphosarcoma of tonsil, neck, metastatic growth size of child's head above scapular region; another size of hen's egg, left cervical region; deglutition almost impossible, patient nearly moribund; Fowler's solution injected, *caused abscesses: erysipelas on neck; tonsillar growth disappeared, larger mass decreased markedly to size of pigeon's egg, those at base of tongue to hazel nuts*; recurrence in 4 weeks; *erysipelas inoculated, causing well marked infection on trunk; again almost complete regression occurred*: further recurrence and metastases, disease progressed, death from hemorrhage. (383; 566; 583).

12. (*Wyeth*) L Male, aged 60; lymphosarcoma neck, far-advanced, general condition poor; *severe erysipelas, causing death on 3rd day; no apparent effect on tumor.* (583; 946, p. 986).

SERIES A, GROUP 4, FAILURES

13. (*Eliot*): Female adult; recurrent mammary carcinoma; *erysipelas; marked decrease in size, great improvement in general condition*; improvement lasted 6 weeks, then recurrence; attempts made to induce erysipelas by inoculations, without success; disease progressed, causing death. (123; 125; 583k).

14. (*Achard*): J.P., male, aged 57; cylinder cell epithelioma pyloric region of stomach; multiple metastases to lungs, liver, etc.; general condition poor; developed *abdominal abscess, umbilical fistula; fistula closed; remission of pain, improvement in condition (temporary)*; pain soon recurred, more acute; fistula reopened; patient extremely cachectic, very thin; hard mass size of fist, inguinal and axillary lymph nodes also enlarged; death 2 days after admission; autopsy revealed soft grey encephaloid tumor in pyloric region, *umbilical fistula connected with extensive abdominal abscess, many hepatic metastases; some fatty degeneration of tumor cells apparent*. (2).

15. (*Czerny*): Female adult; many times recurrent mammary carcinoma, chest wall thoroughly infiltrated; 7 operations performed prior to consulting Czerny; he dissected as much as possible of growth leaving wound with carcinomatous base about 15 cm. in diameter; *severe, almost fatal erysipelas infection of wound; carcinomatous nodules regressed completely*; wound healed in 8 weeks; remained well 2 years; then died apparently of bronchopneumonia; chest wall, axilla free of cancer, but right lung contained many metastatic nodules, considered cause of death. (129; 174; 583K).

16. (*Krynski*): Sex and age not recorded; inoperable carcinoma of thyroid, extensively involving throat; upper portion excised to relieve pressure on trachea and impending suffocation; 2 days later severe parenchymatous hemorrhage required reopening of wound; *abundant suppuration followed, lasting many weeks; greater portion of tumor sloughed off, leaving healthy granulation tissue; healing occurred except for small nodule*; patient left clinic apparently well, wound completely healed; recurrence of very rapid growth, death about 3 months later. (260; 413).

17. (*Sauerhering*): Mrs. L., aged 58; very extensive inoperable round cell sarcoma of neck, infiltrating behind sternomastoid and sternum; very little motion of jaw, mastication impossible, deglutition painful; incomplete removal, large vessels and nerves embedded in tumor; *mild erysipelas infection in region of wound, swelling of entire neck, breathing impaired; caused disintegration and liquefaction of tumor; condition improved during and following infection*; later given Coley toxin therapy, causing necrosis; large amounts necrotic tumor tissue curetted under anesthesia, revealed that necrosis of all tumor tissue had occurred; fistula into trachea and esophagus allowed food and air to escape into wound; condition declined rapidly after operation; died inanition, 3 months after infection. (959).

18. (*Richardson*): J.R., male, aged 6; recurrent lymphosarcoma primary in left cervical

SERIES A, GROUP 4, FAILURES

lymph nodes; 16 nodes excised; local recurrence removed a year later; 3rd operation August 1895; axillary metastases appeared soon after, grew rapidly during next year: large lobulated mass involving left axilla, scapula, overlying tissue; October 3, 1895, 4th operation; extensive dissection down to axillary vessels, backward to scapula; disease too extensive for complete removal, surrounded axillary vessels, infiltrated skin; 18 days later *severe infection upper angle of wound, pleurisy, empyema, large abscess over sacrum, condition desperate but patient recovered, remains of growth completely disappeared, tissues entirely normal*; well 18 months, then developed mediastinal metastases, died suddenly August 20, 1899, 7 years after onset, 22 months after infection. (581, Discussion Case 2, 583k; 700).

19. (Korff): Female adult; very extensive inoperable mammary carcinoma involving chest wall, of slow growth, 14 years duration: *typical acute erysipelas, fever to 41.5°C.; tumor tissue became necrotic, extensive absorption degenerated tumor, very extensive phlegmon, sloughing of subcutaneous tissues; patient weakened, died.* (399; 583k).

20. (Oliver): Young boy; inoperable multiple sarcoma of skull, apparently untreated; one of tumors on back of head apparently became infected, *abscess formed, was incised; this tumor disappeared, others grew larger, one began to ulcerate destroying skull, exposing dura matter, infiltrating brain.* Weak solutions of erysipelas serum obtained from Paris then tried with no apparent effect; disease progressed causing death. (613).

21. (W.B. Coley): L.C.F., male, aged 25; extensive inoperable round cell sarcoma involving $\frac{2}{3}$ of left posterior thigh; *onset occurred during attack of influenza; counter-irritants caused pain to disappear*; following a strain, growth increased greatly; potassium iodide given; growth diminished somewhat, then remained stationary; about 18 months after onset *suppuration occurred*; Dr. Rudolph Matas explored mass, referred patient to Coley when tumor was 13 × 20 cm. in diameter; sinuses then freely curetted and enlarged, *dark, foul pus evacuated, temperature 100-104°F. for 10 days*; Coley toxins (Buxton VI) then given for 2 months; no apparent benefit, except that appetite remained remarkably good until shortly before death due to dyspnea. (125; 528).

22. (Hanszel): M.F., female, aged 4; recurrent inoperable round cell sarcoma of tonsil, metastases at angle of jaw; also submaxillary lymph nodes; *peritonsillar abscess (Streptococcus pyogenes and Staphylococcus aureus); perforation to external ear; tumor in throat became necrotic, disappeared; hard submaxillary node remained size of bean*; entirely well for 3 weeks; tumor then recurred, protruding mass in soft palate and tonsil size of apple; incisional biopsy; thereafter tumor grew much more rapidly, requiring tracheotomy; child could no longer close mouth; disease progressed causing death 3 months after infection. Postmortem revealed involvement of tongue, right antrum of Highmore, down to maxillary fossa, main mass filled buccal cavity; *evidence of some fatty degeneration of tumor cells, and anemia*; (compare this case with Case 4, Group 1, Determinate Successes, Biedert's famous case). (310; 583).

SERIES A, GROUP 4, FAILURES

23. (*Kappes & Kraske*): Female, aged 64; extensive inoperable lymphosarcoma involving right axilla, supraclavicular fossa, each mass being the size of child's head, also right cervical lymph nodes (size of walnuts); *erysipelas infection of right forearm lasting 4 weeks during which 3 larger masses decreased from size of child's head to that of goose eggs, cervical lymphadenopathy disappeared*; patient died 5 weeks after onset of erysipelas; autopsy showed *marked necrosis and regressive changes had taken place in tumors*. (373; 583).

24. (*Lewin*): Female adult; inoperable mammary carcinoma; several *attacks of erysipelas caused cessation of growth and regression*; observed for 2 years; later died of another attack of erysipelas. (344, Case 32, Table 3, p. 545; 451; 583k).

25. (*de Beurmann, Bith & Cain*): Ch. H., male 70; inoperable basal cell epithelioma face, involving inferior maxilla, hard palate, recurrent in inner canthus right eye; primary growth removed, extensive resection inferior maxilla, hard palate; recurrence treated by radiation; *facial erysipelas (2 attacks), lesion remained stationary, general condition good for 5 years*, then rapidly declined in next 2 months; death due to 2nd primary extensive cylinder cell epithelioma stomach with liver metastases in the process of colloid degeneration; *death occurred over 5 years after onset of basal cell epithelioma face, the latter was still present, but contained few mitoses*. (184).

26. (*Mitchell*): L.G., male, aged 45; recurrent round and spindle cell sarcoma of thigh with metastases; surgical removal about 6 weeks after onset, considerable hemorrhage, checked with greatest difficulty; wound packed; *mild postoperative infection; recurrence*; Coley toxin therapy: 21 i.m. injections in 42 days; tumor increased in size; *infection and fever for 2 weeks, large amount of discharge from tumor*; death about 4 months after onset, with metastases to lungs, liver, kidneys, mesentery; *no apparent benefit noted from infection or toxins*. (659, Vol. 174, Case 1289).

27. (*Broeckaert*): B.J., male, aged 57; cylindroma of larynx, voice raucous, respiration painful; patient bedridden, condition alarming; *erysipelas infection of larynx, fever*; tumor involved entire epiglottis, tissues surrounding laryngeal cartilages extending into right pharyngeal wall; *hot compresses applied to neck during infection; attempted biopsy revealed tumor had become entirely necrotic, easily removed in 2 or 3 pieces of slough; all respiratory symptoms immediately relieved, deglutition much easier, voice almost normal; regained former health in a few days, larynx clean, no trace of tumor*; slight local recurrence few months later, then very extensive pulmonary metastases, death 4½ years after onset. (71).

28. (*Broeckaert*): Female, aged 50; extensive sarcoma of neck, of vast proportions; *erysipelas caused complete regression*; recurrence and metastases few months later, caused death. (71).

SERIES A, GROUP 4, FAILURES

29. (*Strandgaard*): J.K., male, aged 62; inoperable carcinoma sigmoid flexure of colon, adherent to spine and anterior rectum exploratory laparotomy showed larged arteries involved, infiltration; palliative colostomy done; *10 days later erysipelas on buttocks lasting 3 weeks, very ill; extensive tumors disappeared completely, no longer palpable by abdominal or rectal examination; intense pain also ceased completely; general condition improved extraordinarily*; 3 weeks later symptoms recurred, general condition declined rapidly, death 5 months after primary growth had disappeared following erysipelas. (258; 838, Case 2).

30. (*Most*): Male, aged 44; inoperable sarcoma of kidney, metastasis to femur (spontaneous fracture); May 21, 1921: *concurrent pyogenic infection (non-hemolytic streptococcus and staphylococcus), high fever lasting 4 weeks; during infection femoral metastasis was completely absorbed*; primary nephrogenic growth partially removed 12 months later, death shortly thereafter. (564; 583A).

Note: In 1929 Waldapfel reported 14 cases of cancer of the esophagus and pharynx observed in the Wiener Laryngological Clinic, in which a concurrent erysipelas infection occurred. He cited these as evidence against the curative effect of concurrent erysipelas. He believed that in seven cases the disease accelerated with the infection. In analyzing these cases it will be noted that most of them were far-advanced and cachectic, many had had heavy radiation and in several the infection was rather mild. No details were given in many of the cases as to the extent of the erysipelas, the areas involved or the amount of fever elicited. In one case of carcinoma simplex the growth became necrotic following severe septicemia, and in an advanced lymphosarcoma, the cervical metastases softened and at autopsy following death on the ninth day of the infection, degeneration of the cervical metastases was found. Three cases were not traced for end result. (909).

31. (*Waldapfel*): O.H., aged 46; inoperable squamous cell carcinoma of larynx, swallowing painful; swelling made breathing difficult; tracheotomy required; *fever for some weeks*; a month after tracheotomy necrotic piece of cartilage excised, diagnosed as perichondritis; *erysipelas then developed in tracheotomy wound, fever to 40° C. for 2 weeks; no benefit seen*; biopsy 2 months later, because of "luxurious granulations"; laryngectomy; 6 weeks later recurrent nodule above trachetomy scar; radium, diathermy, x-ray given; disease not controlled; death due to erosion of carotid vessels. (909, Case 1).

32. (*Waldapfel*): P.P., aged 40; slightly protruding inoperable round cell sarcoma of frontal sinus, bony hard; operation; later curettage of luxurious granulations; 6 days later *erysipelas, temperature to 40° C. lasting 10 days; no apparent benefit noted*; patient discharged in 6 weeks; died meningitis 4 months later; autopsy showed extensive metastases in pia mater, brain, skin. (909, Case 2.)

33. (*Waldapfel*): M.F., aged 53; ulcerated carcinoma simplex of roof of pharynx,

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breathing difficult; radium for 2 weeks, striking improvement; 2 months later growth again began to increase in size; radium again applied; within 3 months metastases in right sternocleidomastoid region; considerable x-ray given, slight regression; then developed *erysipelas infection over tumor, abscess on right wrist, left axilla, septicemia; tumor became necrotic, patient became increasingly cachetic*, death 9 months after onset. (909, Case 3).

34. (Waldapfel): .M., aged 53; carcinoma of right piriform sinus, extending into larynx and along jugular vein; radical excision of nodes, tracheotomy performed; *erysipelas 3 weeks later, no apparent benefit noted*; total laryngectomy 3 weeks after recovery from *erysipelas*; small fistula closed by plastic operation; later metastases to supraclavicular region, cachexia, death. (909, Case 5).

35. (Waldapfel): J.F., aged 46; recurrent spindle cell sarcoma of upper pharynx pushing soft palate forward with cervical metastases; biopsy; considerable x-ray and radium, temporary benefit; recurrence and cervical metastases in 1 month; *erysipelas, temperature to 39.9° C., lasting 7 days; no apparent benefit*; during next 2 months increasing pain, metastases to liver, ascites, death. (909, Case 6).

36. (Waldapfel): R.R., aged 41; growth in roof of pharynx, (histologic type not stated); increasing hearing loss; radiation caused slight improvement; condition stationary 5 months; *erysipelas, temperature to 39.9° C., lasting 12 days*; discharged home; *no apparent benefit*; returned in 2 months with hard tumor in right cervical lymph nodes; further radiation; disease progressed, death few months later. (909, Case 7).

37. (Waldapfel): R.J., aged 45; squamous cell carcinoma of left vocal cords and false vocal cords, causing hoarseness, difficulty in respiration and deglutition; tracheotomy required; 10 days later *erysipelas occurred with abscess below right sternocleido muscle which was opened*; tumor biopsied (operation refused) no apparent benefit; x-ray did not control disease, primary increased, metastases to both cervical regions within 2 months, death. (909, Case 9).

38. (Waldapfel): F.S., aged 51; inoperable lymphosarcoma right neck pushing posterior pharynx forward, metastases in right and left supraclavicular regions, right axilla, left inguinal region; biopsy; radium to pharynx; *phlegmonous erysipelas, multiple abscesses on right elbow, gluteal region, fibula and left upper arm; cervical metastases softened somewhat; death on 9th day of infection; autopsy showed "pus-like degeneration of cervical tumors and right submaxillary metastases, as well as tissues between spine and esophagus."* (909, Case 10).

39. (Waldapfel): M.W., aged 43; inoperable epidermoid carcinoma of maxillary sinus, right cheek, hard nodes present below angle of jaw; biopsy; x-ray therapy; *two weeks later erysipelas developed, temperature to 39° C., lasting five days; tumor rapidly increased in size*; external carotid ligated; diathermy given for weeks, later radium; no

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apparent effect; recurrence at root of nose not checked; partial excision, further radium, increasing cachexia, death. (909, Case 12).

40. (*Hoffman*): Male adult; inoperable papillary adenocarcinoma of cardiac end of stomach size of orange, condition far-advanced; *growth disappeared completely following attack diphtheria and administration diphtheria antitoxin*; recurred to former size; *again disappeared following second attack diphtheria*; again recurred to former size; patient then developed *erysipelas*; *growth shrank to $\frac{1}{3}$ its former size*; no surgery or radiation or other form of therapy given in this case; disease later progressed causing death. (589).

41. (*Memorial Hospital*): Mrs. M.K., aged 58; inoperable synovial sarcoma peroneal bursa of right foot (very small spindle cells), metastases in groin, mediastinum, lungs; palliative amputation; *severe gas gangrene infection of stump*, serum given; higher amputation; reactive pneumonitis; death due to tumor, *no apparent benefit from infection*. (589).

42. (*Marsh*): Female, aged 64; inoperable mammary carcinoma, multiple metastases on scalp, prognosis regarded as "few months"; radiation caused rapid dissemination; *facial erysipelas caused remarkable healing of scalp lesions*; 9 injections Coley toxins then given (Parke Davis XIII); another brief course 4 months later; no appreciable effect from toxins; disease progressed causing death. (583k; 589).

43. (*Memorial Hospital*): Mrs. H.H., aged 64; inoperable epidermoid carcinoma rectum, grade II; (date of onset not recorded); exploratory laparotomy, sigmoid colostomy; postoperative recovery only fair (psychological reasons?); x-ray (2400 r): *severe streptococcal sore throat, could not swallow, fed parenterally, hospitalized 10 days; also had macular non-itching, pigmented rash over trunk, neck, extremities*; radium packs February 2 to March 8, 1939 (12,000 mch.) *complete regression*; radiation ulcer causing severe pain required perineal resection of rectum; *tissue showed no evidence malignancy*; metastases left groin; x-ray (2150 r), some decrease in size; improved; disease then slowly progressed, *death 9 years after onset, 7 years after streptococcal infection*. (527; 258; 589).

44. (*Memorial Hospital*): R.J.H., male, aged 14; metastatic osteogenic sarcoma primary in lower femur; incisional biopsy, x-ray (8,000 r tumor dose in six wks.); fell on knee; high thigh amputation 3½ months after onset; pulmonary metastases 15 months later; *furuncle on stump 2 months later; symptom-free next 9 months*; disease then progressed, death 3 years after onset. (527).

45. (*Barling*): Mrs. A.M.J., aged 62; multiple myeloma involving entire skeleton; patient bedridden, with pathologic fractures of several vertebrae; had not been benefited by x-ray or stilbamidine; severe pain for many months, dying; *severe facial erysipelas lasting a week, fever to 103° F.*; "improved out of all recognition, pain-free, able to be

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up with spinal brace"; appetite increased, general condition and morale very good for 22 months, blood chemistry and x-ray appearance of bones unaltered by infection; died of generalized myelomatosis, having again had rather severe bone pain for 2 months prior to death. (349; 583d; 589).

46. (Vogler): Mrs. M.C., aged 57; malignant melanoma of right foot, metastases to right groin, thigh; *primary lesion became infected following trauma*; widely excised 9 months after onset; pathologist reported "marked evidence infection, areas of atypical keratoses," 3 weeks later groin dissection revealed metastatic areas in nodes; amputation refused; free from disease 11 months, then further metastases to right thigh; biopsied; further metastases in right leg and thigh in next year; again refused disarticulation; not seen again for 2 years; *during this interval all but one metastatic lesion regressed spontaneously*; another lesion appeared in October 1953, this and other one excised; June 1954, numerous nodules present on right leg, one excised; 22 others given 1,000 r x-ray (low voltage) in 20 days; all regressed including some untreated nodules; no further lesions developed for 2½ years, then another appeared, was excised; well March to December 1958 when *large pleural effusion occurred*; Papanicolaou smears, Class I; nitrogen mustard given early 1959; *cystitis early 1959; thereafter Pap. smears were negative for tumor*; disease reactivated, died widespread metastases, September 1959, 11½ years after onset. (257; 589; 902).

47. (Morganstern): Mrs. B.S., aged 31; inoperable adenocarcinoma of head of pancreas, involving duodenum; onset during 4th pregnancy; premature delivery, October 10, 1952; *puerperal fever, temperature to 104°F.*; 3 days post-partum became deeply jaundiced, clay colored stools, anemia; lost 22 lbs. in weight; exploratory laparotomy revealed diffuse mass size of orange in head of pancreas, nodule in duodenum; latter removed for biopsy; gall bladder greatly distended, cholecystostomy (drained 650 cc. bile daily); patient gained weight; January 19, 1953; radical removal attempted; *no modification of primary mass seen but liver and gallbladder much smaller*; extensive metastases along lymphatics, one egg-sized; radical removal impossible; cholecystogastrostomy; *postoperative wound infection, fever (to 103°F.) lasting 10 days, drainage through cigarette drain in wound, also had inflammatory reaction in deep muscular area due to nylon suture*; by February 23, 1953 *no clinical evidence of disease apparent*; Coley toxin therapy then given (20 i.m. injections in 4 weeks); gained 9 lbs., condition satisfactory, June 1953; 2nd course toxins (15 doses); disease not controlled; developed pyloric stenosis requiring gastroenterostomy November 1953; death April 1954, nearly 2 years after onset. (589).

48. (Ross-Loos Medical Group): Mrs. J.Z., aged 28; terminal infiltrating duct carcinoma of left breast, extensive skeletal metastases to lumbar spine, sacrum, ribs, pelvis, right leg, with pathologic fracture of femur; onset occurred in early June 1955, in 6th month of 3rd pregnancy (in a period of 3½ years); July 22, 1955: radical mastectomy; deep x-ray (12,000 r); child born at full term; back pain June 1956, a year after onset, ceased after vitamin injections; severe back pain recurred early 1957 at each menses; June

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1957, extensive skeletal metastases as stated above; testosterone gave good initial pain relief for few weeks; femoral fracture then occurred; pinned; October 1957, bilateral oophorectomy, little improvement; lost 85 lbs., bedridden; March 1, 1958, *developed urinary tract infection*; neurogenic bladder, due to metastases; March 10, 1958: *acutely ill, fever due to pyelonephritis, w.b.c. 11,500; pain ceased*; x-ray to chest caused severe pain late March 1958; *2 more attacks pyelonephritis, high fever; each time these occurred pain ceased as it had after first episode; by August much improvement noted, had gained 25-30 lbs.*; began to fail late fall 1958, death March 7, 1959, over 4½ years after onset. (583k; 589).

49. (*Myre*): Male adult; terminal, generalized lymphosarcoma; biopsy, sent home to die, generalized lymph node involvement with palpable abdominal masses; *developed fever, severe Pseudomonas aeruginosa bacteremia* (blood cultures), causing shock; by July 31, 1955, *nodes in left inguinal region had liquefied, 48 hours later those on right side had also liquified, fluid easily aspirated, plated, failed to show growth; only palpable evidence of liquefaction occurred in inguinal nodes*; infection caused death in about 10 days. (589).

50. (*Jenkins*): O.J.K., male, aged 57; hypernephroma left kidney with invasion of pelvis and blood vessels, metastases to both lungs; sudden onset, severe pain in left flank October 26, 1950; nephrectomy November 2, 1950; pathologist reported presence of *chronic nephritis, not clinically apparent prior to operation*; patient returned to work; during next year films showed increase in size and number of metastatic nodules in lungs, (wife had committed suicide 7 months after his nephrectomy due to worry over his cancer); general health remained good; May 24, 1954 readmitted for larger perforated gastric ulcer and stenosing duodenal ulcer; *chest films showed marked regression metastatic nodules in lungs*; June 24, 1954: partial gastrectomy, posterior gastrojejunostomy; pathology: gastric ulcers, benign, active; *in excellent health, lung metastases continued to regress, leaving 1 small nodule*; recurrence in scar, October 1959, 9 years after nephrectomy; excised; well until February 1963, further local recurrence too extensive to remove; biopsy; x-ray therapy; disease progressed, generalized metastases, marked cachexia; *severe lobar pneumonia (terminal staphylococcic)*; death June 26, 1963, over 12½ years after onset; autopsy showed arteriosclerotic heart disease, metastasis to right flank, parietal pleura, mediastinal lymph nodes, diaphragm; *latter contained necrotic tumor tissue*. (361; 362; 583a; 589)

51. (*Graham and Coleman*): Female, aged 63; metastatic anaplastic carcinoma proximal third left humerus (primary site unknown); onset, 1951 "rheumatism" of left shoulder, malaise for many months; then developed fever, but no diarrhea or G.I. symptoms; aspiration of soft area of lesion yielded *frank pus (Salmonella montevideo)* provisional diagnosis: *salmonella osteomyelitis; chloramphenicol given; organisms rapidly disappeared from stools but pain and swelling of shoulder continued; exploratory operation revealed proximal 1/3 humerus invaded by neoplastic mass; wound discharged pus (S. montevideo)*; patient died 3 months later; *no apparent benefit from infection*. (294).

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52. (*White Plains Hospital*): W.A.G., male, aged 50; large poorly differentiated adenocarcinoma completely encircling ascending colon, multiple metastases to mesenteric lymph nodes, single metastasis 4-5 cm. in diameter in right lobe of liver; 1954, 1st divorce, psychiatric treatment; low basal metabolism 1957, 1 or 2 gr. thyroid given thereafter daily; onset, summer 1961 during 2nd divorce proceedings, psychiatric treatment: lethargy, impaired mental function, poor concentration, 10 lb. weight loss in month prior to January 10, 1962; complete physical examination including sigmoidoscopy then negative; given steroids August, September 1962 for 2 episodes low back pain; by late September 1962 vague abdominal pains, anemia, dyspnea; 5 lb. weight loss in week prior to admission, October 5, 1962; barium enema revealed carcinoma ascending colon; Vitamin K, transfusion, antibiotics given prior to surgery, October 11, 1962; 6 cm. annular tumor encircled bowel below hepatic flexure, extending well into surrounding fat, metastases in adjacent nodes, mesentery; *intense inflammatory reaction in region of invasive tumor, with abscess deep to the tumor, appendix large, swollen but histologically normal*; end-to-end ileotransverse colostomy performed, omentum over right colon resected, local metastases in mesentery removed, liver metastasis not touched; terramycin; slight fever, 100.4 °F - 101 °F.; October 21, 1962, small bowel obstruction proximal to ileotransverse colostomy required reoperation, ileostomy; *much reaction present around anastomosis; post-operative fever, 102.4 °F., 1.l.q. pain*; discharged November 18, 1962, prognosis, 6 months; gained 16 lbs., returned to work in 1 month, "never felt better"; very active in job and outside activities; against physician's advice married August 1963, adopted wife's 3 children; she had miscarriage November 1963; January 1964 small prepyloric ulcer, improved under bland diet; hemorrhoidectomy summer 1964; by fall 1964 fatigue again noted, also muscle pain, wasting, Dupuytren's contractures of hands, appeared chronically ill; required Dextrodrine or Ritalin to function minimally; appetite decreased; January 1965 again consulted psychiatrist, "cleared as to emotional factors for these symptoms"; by March 1965 fatigue, muscle aching in back, shoulders, difficulty in concentration had all increased; then had thorough work up at Memorial Hospital: n.e.d. clinically and biochemically, condition regarded as due to "anxiety state, gastric ulcer"; fatigue increased more markedly by June 1965, also weight loss, dark brown urine, jaundice, confirmed by liver function tests; final operation August 3, 1965, following aspiration biopsy of liver; 8-10 cm. metastasis found over dome of liver, obstruction intrahepatic biliary system; gallbladder and common duct collapsed; dense adhesions freed, liver mobilized downward, *n.e.d. other than this single large lesion from which several biopsies taken*; 5 FU given for about 1 month ending September 29, 1965, 2 more vials given in November 1965; bilirubin remained remarkably elevated on discharge, weight had declined to 132 lbs. (40 lb. loss); prognosis regarded as about 2 weeks; returned home, able to be up and about, but not able to work thereafter, not bedridden until final 5 days; terminally had nausea, vomiting, weakness, pain and edema of lower extremities; death June 26, 1966, about 5 years after onset. (258; 589).

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53. (Kolar, Bek et al.): M.K., male, aged 55; hypernephroma right kidney, multiple metastases in both lungs, enlargement lymph nodes in both hilae; onset, spring 1958, 1st of 3 episodes right renal colic; 1st seen February 1959 after 3rd attack renal pain; fist-sized mass present in right hypogastrium, metastases as noted above, palliative nephrectomy April 30, 1959; *postoperatively developed 2 fistulae which discharged pus for 5 weeks; moderately febrile for 4 weeks (to 38.3 °C.);* cachectic, but no pain; given vitamin B and iron; *by mid-summer 1959 all but largest pulmonary metastases had regressed; complete disappearance of this lesion apparent by October 1959, 6 months after nephrectomy;* n.e.d. thereafter, gained 16 kg., in good health until skeletal metastases early 1970, rapid downhill course; death six months later; autopsy: no local recurrence or lung involvement. (237; 354; 393; 583a; 589).

EFFECTS OF NON-PYOGENIC INFECTIONS: SERIES B

Introduction

Series B consists of the published or unpublished cancer cases in whom a non-pyogenic infection developed concurrently, a total of 58 patients. Of these, 49 were inoperable (many with metastases) and nine operable when the infection occurred. The diagnosis was confirmed histologically in the majority of these cases.

A comparative analysis has been made of these 58 cases with those in which *pyogenic infections* occurred (Series A, inoperable 158 cases; Series C, operable, 116 cases.)

It is apparent that the non-pyogenic infections were rarely as effective as the pyogenic in producing complete regressions and permanent results either in inoperable or operable neoplasms; nor in preventing recurrence following surgery for cancer. Apparently a pyogenic wound infection following surgery for cancer was Nature's form of adjuvant therapy!

Fourteen patients in Series B remained free from further evidence of their neoplasms five to 48 years after onset. *Six of these were children under five years of age* (see cases 17, 34, 35, 37, 45, and 51, three boys and three girls.) Of these, five had neuroblastoma, the sixth (case 37) had fibrosarcoma of the thigh (Grade III) with lung metastasis.

One other child with neuroblastoma remained apparently free from disease three years after onset when reported by Rocher (case 11). Attempts to trace this patient subsequently were unsuccessful. Since several authors believe that a one year survival in children with this neoplasm is equivalent to almost five years in adults with other types of tumors, this additional case may be regarded as a permanent result.

Of the eight adults traced at least five years free from recurrence or metastases (Cases 11, 19, 24, 33, 55, 56, 57, and 58), three had extensive metastases, three were operable, and one (case 24) had toxin therapy which caused complete disappearance of her recurrent inoperable lymphoma of the maxillary sinuses. Pulmonary tuberculosis developed after this had occurred. One adult, amputated for osteogenic sarcoma in 1929, remains alive and well in 1977, 49 years after onset, but his pulmonary metastases did not regress completely (case 11).

Of particular interest is case 58, an extensive inoperable, highly differentiated carcinoma of the lung with many metastases to the pleura. This 37 year old man had infection (chill, pneumonia, pleural effusion, w.b.c. 23,600) prior to surgery, plus fever to 103°F. for two weeks following exploratory thoracotomy, during minimal palliative radiation therapy (1200 r tumor dose). These "complications" helped potentiate his response to the radiation. His very positive attitude, upon discharge, included self-imposed hyperalimentation and healthy life style, and these also may have helped increase his immune responses to his tumor. He gained 40 pounds, all evidence of disease disappeared and he remained well when last traced over 10 years later.

In addition to these long term survivors, five other adults were traced well 2-3½ years, and a woman and an adolescent boy remained well "several years." These may

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all have been permanent results. One adult died almost three years after onset of cardiovascular disease (case 16).

In addition to the above patients in whom the disease appears to have been entirely eradicated, there were nine patients in whom the malignancy appears to have run a much slower course than is usual and the patients died over five years after onset (cases 7, 13, 14, 15, 25, 26, 29, 33, 47, and 53), possibly due to the concurrent infection stimulating the patient's resistance to the tumor. In cases 24, 33, and 47 the patients also received injections of Coley toxins and it is difficult to judge the effect of the infections in these cases. In three patients death occurred as a result of the concurrent infection (cases 18, 20, and 23).

As to palliative or temporary effects observed in this series, complete regressions occurred in 28 cases.

It is of course important to stress that various forms of treatment were given to these patients, and that the concurrent infections may have exerted only an additive effect, in most cases in favor of the host, in others in favor of the tumor. For examples of the latter, in Cases 46 and 54, completely quiescent mammary carcinomas were violently reactivated by a concurrent virus infection (grippe, influenza) and in Case 44, a six year old child, the neuroblastoma was recognized immediately following grippe and parotiditis infections. In Case 40 a rapidly growing mammary adenocarcinoma developed immediately after influenza. In Case 43, Rubens Duval reported that a concurrent grippe had a "most grievous effect upon the evolution of the cancer." A similar effect was reported by Home following pneumonitis (Case 7). Cohen, in citing Case 54 stated that viral infections cause lymphopenia and may depress reticuloendothelial activity (118). On the other hand, pyogenic infections and inflammatory episodes are known to stimulate the RES.

These data suggest that the type of concurrent infection listed in Series B may occasionally stimulate the natural resistance of patients with various types of malignant disease, especially children under five years. In young subjects the immune responses are apparently more easily activated and these infections may have helped the patients to respond to the palliative therapy most of them received, i.e., vitamins, small amounts of radiation, biopsy. The effects of the acute inflammatory episodes some of these children sustained as a result of their infections, i.e. severe diaper rash following diarrhea, and severe penicillin dermatitis (Case 35) may also have played a role in activating the RES.

It would seem that one should avoid giving cancer patients antibiotics or anti-inflammatory drugs in the future, not only because infections may cause regression or remission but because these drugs may alter the tumor-host relationship in favor of the tumor. It is now well known that many antibiotics have a depressing effect upon the hematopoietic and reticuloendothelial systems. One must consider that patients with concurrent infections of whatever type that are aggressively treated with antibiotics, may not exhibit the beneficial effects upon their neoplasms that were seen in the earlier period in which no antibiotics were used.

SERIES B: NON-PYOGENIC

Group 1. Mostly inoperable cancer in which non-pyogenic infections or inflammation developed spontaneously causing complete regression of the primary and/or metastases. Traced five or more years after onset.

Type of Infection

- 1 diarrhea, acute bronchitis, etc.
- 2 diarrhea and diaper rash
- 1 chicken pox
- 1 infected acne, influenza, U.R.I.
- 1 severe respiratory infection, cough, sore throat
- 1 pneumonitis, leukocytosis
- 1 pneumonia, several attacks
- 1 pneumonia, fever to 103°F., leukocytosis (to 23,600) pleural effusion

Type of Tumor

- fibrosarcoma
- neuroblastoma with metastases
- neuroblastoma with metastases
- neuroblastoma liver enlarged
- hypernephroma, multiple metastases, lungs
- osteogenic sarcoma, metastases lungs
- neuroblastoma, inoperable
- extensive epidermoid carcinoma lung, pleura, multiple metastases

Group 2. Inoperable cancer in which non-pyogenic infections developed, caused complete regression but patients not traced or died from other causes less than five years after onset, i.e. indeterminate.

Type of Infection

- malaria
- acute lung infection
- tracheobronchitis
- few attacks bronchitis
- syphilis
- cholera, rubeola, otitis media
- typhoid
- severe ptomaine
- severe grippe
- measles
- smallpox
- mumps
- tracheobronchitis

Type of Tumor

- scirrhus cancer breast recurrent
- sarcoma breast, multiple subcut. metastases
- hypernephroma, lung metastases
- neuroblastoma
- recurrent cancer breast, axillary metastases
- lymphadenoma both orbits, generalized
- extensive lymphosarcoma cervical nodes
- extensive intra-abdominal growth
- far-advanced cancer in mouth
- inoperable tumor of maxilla
- carcinoma face
- retinoblastoma
- hypernephroma, lung metastases

Group 3. Incomplete regression not traced five years.

Type of Infection

- miliary tuberculosis
- dysentery

Type of Tumor

- very extensive intra-abdominal tumor
- inoperable gastric cancer

SERIES B: NON-PYOGENIC

Group 4. Deaths: Inoperable cancer in which concurrent non-pyogenic infection developed (note prolonged survival in several cases).

<i>Type of Infection</i>	<i>Type of Tumor</i>
violent pneumonitis	breast cancer, clavicular metastases (9½ yrs.)
pneumonitis	breast, axillary and skin metastases (4½ yrs.)
pneumonia	lymphosarcoma tonsil, pharynx, cervical metastases
pneumonia	hypernephroma, lung metastases (9 yrs.)
pneumonia	adenocarcinoma liver, regional and brain metastases (4 yrs.)
pneumonia	multiple myeloma
acute pulmonary tuberculosis	ulcerated recurrent scirrhus breast (died tuberculosis)
pulmonary tuberculosis, bronchitis, pleurisy	large scirrhus breast (6 yrs.)
miliary tuberculosis	thrice recurrent very extensive cancer en cuirasse breast, completely regressed, died infection
pulmonary tuberculosis	inoperable carcinoma thyroid (6 yrs.)
typhoid	spindle cell sarcoma parotid (5 yrs.)
severe colitis (also Coley toxins)	papillary cystadenoma ovary multiple peritoneal implants (11 yrs.)
diphtheria	adenocarcinoma stomach
influenza	hepatoma
virus pneumonia	recurrent adenocarcinoma of colon (6 yrs.)
grippe, parotiditis	neuroblastoma
serum hepatitis	multiple myeloma (4 yrs.)
measles	lymphosarcoma (8 yrs.)
grippe	adenocarcinoma of the stomach

Group 5. Operable cancer with concurrent non-pyogenic infections.

A. Traced well five or more years after onset:

<i>Type of Infection</i>	<i>Type of Cancer</i>
pulmonary tuberculosis (developed after inoperable tumor had disappeared under toxin therapy)	malignant lymphoma antrum, ethmoid
Salmonella barielly in tumor area	adenocarcinoma rectum at junction of sigmoid

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cat scratch fever
 serum hepatitis (also had low-grade
 subphrenic abscess)
 serum hepatitis
 serum hepatitis

adenocarcinoma colon
 leiomyosarcoma stomach, colon, ex-
 tensive metastases
 undifferentiated epithelioma bronchus
 epithelioma bronchus

B. Traced well three to five years:

Type of Infection

malaria
 malaria
 malaria
 tracheobronchitis

Type of Tumor

epithelioma lip
 pavement cell epithelioma vagina
 extensive hypernephroma
 hypernephroma, multiple lung
 metastases

C. Complete disappearance, not traced:

Type of Infection

severe malaria

Type of Cancer

epithelioma lip

D. Died

Type of Infection

virus pneumonia

Type of Cancer

recurrent adenocarcinoma colon,
 metastases

*Group 6. Cases in which concurrent virus infections appeared to stimulate the onset
 or growth activity of the neoplasm:*

Cases 41, 42, 43, 46, 54

SERIES B: NON-PYOGENIC

This series of 58 cases developed non-pyogenic infections before, during, or immediately after treatment for various types of malignant tumors. The diagnosis in most cases of these cases was confirmed histologically. The name in parenthesis following the case number refers to the physician, surgeon or hospital handling the case. The abstracts are listed chronologically within the various types of infections. At the end of each abstract the bibliography reference numbers indicate where more details may be found. Detailed histories of most of these cases are available at the Cancer Research Institute.

Malaria: 5 Cases

1. (*Trnka*): Female, adult; recurrent inoperable scirrhus carcinoma of breast; mastectomy; much later recurrence involving entire other breast; mercury, internally, externally, no benefit; *then developed double tertian malaria; in a few weeks whole scirrhus cancer disappeared*. Case also observed by Coliny and cited by Loeffler who stated: "This observation opens a new field for the treatment of cancer. Our knowledge of malaria makes it possible to induce it as a therapeutic agent by injecting the blood of malarial patients, either subcutaneously or intravenously, and to control induced malaria safely with quinine. We can abruptly terminate such malaria at any time if dangerous complications were to be feared." In Loeffler's opinion we can, without hesitation, inoculate cancer patients with malaria, and he suggested that such clinical investigations be undertaken. Apparently a very few cases were so treated, chiefly by Braunstein in 1931. (463; 583K; 877)

2. (*Portanova*): Male, adult; epithelioma lower lip, August 1902 developed *severe malaria concurrently; marked regression, softening then completely disappeared*; recurrence, excision; end result unknown. (677)

3. (*Avromovici*): Male, aged 45; epithelioma of lower lip of 2 mos. duration; zinc oxide cauterization, no benefit; poor general health; developed *tertian malaria, fever 40°-41° C., lasting 7 wks.; quinine given, complete regression, general health improved*; no recurrence; traced well 3½ yrs. later. (15)

4. (*Jovin*): Female, aged 45; extensive pavement cell epithelioma of vagina; radium given for 5 days, caused slight regression; biopsy showed tumor was not undergoing radio-necrosis; developed *malaria, daily fever for 3 wks.*; antimalarial therapy then instituted, causing prompt cure of the fever; *epithelioma regressed completely, left tissues soft, supple*; well and free from recurrence 3 yrs. later. (371; 583j)

5. (*Sabadini*): Male, aged 32; extensive cystic carcinoma lt. kidney; mass in lt. side developed at age 10; also had *concurrent rather severe malaria*; 3 episodes pain, hematuria 1941-1944, January 1945; x-rays showed small calcifications in lt. lower ileolumbar region; by January 1945 enormous, smooth mass present in lt. side extending from

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iliac fossa across mid line, pyelograms indicated enormous mass attached to lt. kidney was neoplastic; explored, biopsy; pathologist reported massive areas of more or less hemorrhagic necrosis in extensive epithelioma; 5 days later, nephrectomy; *febrile for 6 days after 2nd operation*; x-ray therapy given prophylactically (2 cycles); *no further evidence disease*; *reported well 2 yrs. after surgery* and 22 yrs. after onset of tumor. (583a; 757)

Bronchitis, Pneumonia or Pneumonitis: 13 Cases

7. (Home): Female, aged 57, prior to 1832; inoperable cancer breast, involvement of clavicular nodes; untreated; *developed violent pneumonitis*; on recovery, *tumor became very large*, another formed between breast and clavicle, and 2 smaller nodules above it; ulcerations; pain; *disease progressed slowly*, causing death at the end of the 9th year. (338; 583k)

8. (Home): Female, aged 37, prior to 1830; inoperable cancer breast, axillary and skin involvement, of 4 yrs. duration; *pneumonitis then developed*; *from this time on she never noticed her breast, in which symptoms remained stationary*; death 4 mos. later. (338; 583k)

9. (Kutzner): Female, aged 18, 1889; round cell sarcoma breast, multiple metastases in subcutaneous tissues; patient developed *acute lung infection (pneumonia?)*; *all neoplastic deposits disappeared*; *not traced subsequently*. (416; 583k; 717)

10. (Coley): D.C., male, aged 44; recurrent lymphosarcoma tonsil and pharynx, metastases cervical nodes; Coley toxins and radiation given, disease not controlled, prognosis hopeless; patient then developed *pneumonia, fever 104° F.*; *markedly enlarged nodes in both cervical regions disappeared*; *no evidence of disease in tonsil, pharynx or neck*; recurrence within a month; disease not controlled; death. (123)

11. (Speed): J.D., male, aged 21; osteoblastic osteogenic sarcoma of right femur, with roentgenological evidence possible single pulmonary metastasis; onset, August 1928, lost 30 lbs. in 9 mos.; continuous pain; May 10, 1929 amputation, 9 mos. after onset; extensive pulmonary metastases present March 1, 1930; still more present July 29, 1930; also uniform clouding upper left lung; *from March 1930 to April 4, 1942 had recurrent attacks mild dyspnea, cough, bloody sputum, with leukocytosis* (to 14,100); no sustained weight loss, no tubercle in sputum; by April 1942 *metastases had become smaller and less dense*; alive and very well 1977, 49 years after onset. (583h; 589; 820)

12. (Rocher): H.C., female, aged 6 mos.; inoperable sympatheticoblastoma, apparently arising in the presacral sympathetic trunk; extensive mass obstructing entire hollow of pelvis extending from posterior sacrum almost to posterior pubis; retention of urine

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developed on 8th day after birth; slight erosion of anterior first sacral vertebra; exploratory operation, condition hopeless; segment removed for biopsy; while hospitalized had *few attacks bronchitis*; no further retention of urine after 1st day; x-ray (1800 r posterior, 1080 r anterior pelvic region, 180 KV); *steady complete regression in next 3 mos.*; no recurrence or metastases 3 yrs. after onset. (259; 713)

13. (*Garland*): Male, aged 61; multiple myeloma, myeloblastic type, involving T8 vertebra, lt. 8th rib, pelvis, rt. femur, with flaccid paralysis both legs, bladder difficulties; just prior to onset developed *lobar pneumonia, pleural effusion, lung abscess, fever to 103.6°F.*, hospitalized May 1 to July 15, 1939; about July 1, 1939 onset abdominal pain, post-prandial distention; about September 1, 1939, numbness over abdomen, legs, stiffness of legs; 3 wks. later paralysis, bladder difficulties, by October 1939 x-rays showed destructive lesion, compression of body T8, large expansile lesion lt. 8th rib, several small areas decreased density in pelvis, rt. femur; posterior shell cast applied, rib biopsied; x-ray to thorax (3,000 r centered over T8; gradual improvement, able to walk; lost to follow up, believed dead; 18 mos. later returned with stiffness lt. foot, back pain; margins of T7 and T9 now involved, *large rib lesion had partially regenerated*; 2nd cycle x-ray over T8 (2100 r); gained weight; final x-ray October 1941 (600 r); November 1941 cast again applied to lower thorax and abdomen for 2 mos.; improved, did well except for *another attack of pneumonia July 1942*; worked as night watchman; urine remained negative for Bence Jones protein; spine, rib lesions partially recalcified, but many new radiolucencies apparent in skull, spine, ribs, pelvis, upper femora; however, *continued to look and feel well, 1947*; died May 2, 1948, *rt. lobar pneumonia*, almost 9 yrs. after onset. (277; 583d)

14. (*Memorial Hospital*): J.P., male, aged 5; Ewing's sarcoma 8th rib; onset spring 1949, following bronchitis (given penicillin); *pneumonia, pleurisy* September 1949, November 1949 *another U.R.I.*, given penicillin tablets; rib resected November 1949; *fever to 103°F.*; *wbc 14,000*; combined HN₂ and x-ray (2000 r tumor dose); 2 transfusions; January 1950 further radiation (1025 r tumor dose); *in excellent condition next year*; between June 1951 and October 1951 had *4 attacks severe tonsillitis*; tonsillectomy November 23, 1951; *pneumonitis*, August 1952; *diarrhea with fever for 2 wks.* (terramycin, penicillin, aureomycin); radiation fibrosis and dyspnea of radiated lung, pneumonectomy considered to protect good lung from chronic bronchitis; *another U.R.I.* January 1953, (aureomycin, penicillin); metastases to skull; x-ray (3000 r); *complete regression*; well 4 mos.; headache, eye symptoms; further x-ray (2600 r); again improved; lung metastases; death over 6 yrs. after onset. (583b; 589)

15. (*Gonick & Jackiw*): H.J.M., male, aged 58; clear cell adenocarcinoma rt. kidney, metastases lt. lung; onset, August 1949, mass to rt upper quadrant, diagnostic tests refused; nocturia twice in next yr.; about July 1, 1950, epigastric pain; 6 wks. later mass in rt. kidney evident, *wbc 10,600*; pulmonary metastases especially in lt. lung; rt. transperitoneal nephrectomy; large fungating tumor found; lt. thoracotomy 1 mo. later lingular and 3 metastatic nodules from lt. base removed; *mild fever for 2 wks.* (99°-

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100° F.); suspected nodules in rt. lung increased at 1st then regressed and disappeared by August 1951, but a nodular lesion reappeared on rt. lung; January 1947, fever, chills, night sweats, cough, productive of ½ cup white sputum, consolidation rt. upper lobe, hilar rt. mass evident; at bronchoscopy a 5 mm. mass noted, obstructing rt. upper lobe bronchus; biopsy reported as *granulation tissue, with inflammatory cells*; antibiotics given, without apparent effect; 4 mos. later hemoptysis, lb. wt. loss; *wbc 11,300*; another biopsy negative; admitted to another hospital with cough, diarrhea, fever; chest films showed hilar mass with cavitation; antibiotics for 11 days; again hospitalized August 1958 for "grand mal" seizures which ended in coma and death; chest film showed lobulated area of increased density in entire upper half rt. lung, also 4 × 8 cm oval density projecting medially from rt. lateral chest wall; no postmortem; died 9 yrs. after onset, 8 yrs. after nephrectomy. (288a; 583a)

16. (Hallahan): Male, clerk, aged 75; hypernephroma lt. kidney and perirenal fat with 5 or more metastases in both lungs; onset, January 1956, pain, much flatus, hematuria, sputtering urination, clots; pre-operative transfusion 500 cc whole blood; rt. nephrectomy February 1956; given iron for 6 wks.; returned to work; 6 mos. later *tracheobronchitis, penicillin given parenterally; chest films clear August 3, 1957; lung metastases had disappeared*; did not miss a day at work until death October 3, 1958: congestive heart failure due to arteriosclerosis and hypertensive cardiovascular disease. This was nearly 3 yrs. after onset. Autopsy showed no evidence malignancy. (308a; 583a)

17. (Knudsen & Amromin): V.D.H., female newborn infant; inoperable neuroblastoma liver (very large abdominal mass), primary site undetermined; explored at age of 25 days: liver almost completely replaced by tumor; x-ray (1600 r) stopped because of leukopenia, anemia; mass in lt. neck, swelling lt. arm then noted; chlorambucil given without effect; atelectasis, *pneumonia recurred several times in next few months*; beginning September 1955, Vitamin B-12 given (1000 micrograms daily, i.m.); *during next 9 mos. abdominal mass regressed, no longer palpable by June 1956*; May 1956, biopsy of lt. axilla revealed large lobulated mass in superior and lt. mediastinum connecting via apex lt. chest with mass in neck and swelling of arm; it was adherent to ribs and enveloped lt. thoracic and cervical sympathetic chain; portions removed for biopsy, proved to be ganglioneuroma; Vitamin B-12 continued total of 21 mos.; February 1957, liver biopsy revealed extensive fibrosis, no residual neuroblastoma; further stigmata of Von Recklinghausen's disease evident: café au lait areas all over her body, 1956; enlargement of clitoris, 1962; *no further evidence neuroblastoma, alive and well*, attending school, normal intelligence, 1973, 18 yrs. after onset. (259, 389; 589)

18. (Legier): Male, 57, inoperable bile duct adenocarcinoma; liver, regional and brain metastases; onset 1958 (exact date not recorded); at exploratory laparotomy, January 1959, fist-sized tumor present in anterior dome, many satellite nodules along posterior margin; pancreas, regional nodes grossly involved; main mass in liver biopsied; no treatment given; during next 2 yrs. liver reduced in size, general health good; well until fall 1962, then cerebral metastases (nausea, emesis, confusion, dizziness, diplopia,

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ataxia) became comatose; hospitalized, November 10, 1962; *terminal bilateral lower lobe pneumococcal pneumonia and pleurisy*; death 5 days later; at least 4 yrs. after onset; autopsy showed soft, spongy metastatic mass 5 cm in diameter in lt. cerebellar hemisphere, *mostly necrotic, except for outer rim of viable tumor*; atrophy, massive scarring lt. lobe, small separate scar in dome rt. lobe, sites of metastatic adenocarcinoma that regressed spontaneously following biopsy. (436)

19. (Miller, Woodruff & Gamacorta): Male, aged 57; hypernephroma rt. kidney, bilateral pulmonary metastases; appendectomy, 1913; tonsillectomy, 1924, onset 1959, rt. chest pain, region 7th, 8th ribs occurred concurrently with *severe respiratory infection, cough, sore throat, fever, general malaise*; antibiotics, only slight improvement; chest films revealed bilateral pulmonary metastases up to 6 cm. in diameter in both lungs; pyelography revealed mass in upper rt. kidney; rt. transperitoneal nephrectomy; *pathologist reported necrotic tumor 6 cm. in diameter, interstitial tissue fibrotic, infiltrated with aggregates of lymphocytes*; 3 mos. later chest films showed almost complete disappearance of the multiple lesions, *n.e.d.*, in good health thereafter, last traced well August 1967, 18½ yrs. after onset. (542a; 583a; 589)

Pulmonary Tuberculosis: 7 Cases

20. (Paget): Female, aged 25, 1850; ulcerated recurrent inoperable scirrhus carcinoma breast, axillary metastases, disease progressed unfavorably for 12 mos.; patient then developed *acute pulmonary tuberculosis*; *ulcer began to heal, in 6 mos. nearly complete healing*; *large mass metastatic nodes in axilla reduced to 1 hard lump*; patient died pulmonary tuberculosis 6 mos. after cancer had nearly healed (confirmed by autopsy). (623; 624)

21. (Sibley and Laurence): Female adult; inoperable scirrhus carcinoma breast size 2 large oranges, of 6 yrs. duration; hospitalized; *ulceration, sloughing caused almost complete destruction original growth, ulcer almost completely healed*; rapid recurrence, also bronchitis, pleurisy; both tumor and chest symptoms increased, death. Autopsy: *pulmonary tuberculosis in both apices (also beneath pleurae)*; malignant character of tumor also confirmed. Comment: the chronic pulmonary TB may have slowed the progress of the breast cancer prior to admission. The sloughing occurred after hospitalization (indicates some local infection of the ulcer; hospitals in 1858 were not aseptic). *Note the recurrence regressed during the final acute phase of pulmonary tuberculosis.* (430)

22. (Mastin): L.W., female, aged 36; very extensive inoperable intra-abdominal tumor 28 × 8½ cm. in diameter, very vascular, infiltrating in all directions; concurrent *miliary tuberculosis, severe hemorrhages*, a moderately large one several days prior to exploratory laparotomy, excessive hemorrhage, difficult to control; *fever 101° F. 2nd day*; pulse weak, attack of surgical mania on 12th day; *growth decreased 9 cm. in 6 days*,

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gained weight, strength; felt very well; tumor stationary few mos. later; end result unknown. (513)

23. (Sigg): Female, aged 33; thrice-recurrent inoperable adenocarcinoma of breast: extending from sternum over left clavicular region to scapula and left arm; articulation of left shoulder impossible; metastatic mass in axilla; developed *pulmonary tuberculosis, followed by rapid decrease in infiltrating "cancer-en-cuirasse"*; *entire area had regressed completely some days before patient succumbed to pulmonary tuberculosis; great loss of weight during period of regression, axillary metastases reduced from size of fist to size of nut; postmortem showed fatty degeneration of tumor cells in axilla. (796)*

24. (Harmer): L.P., female, aged 44; twice recurrent inoperable malignant lymphoma involving antrum, ethmoid, right superior maxilla, posterior septum and nasopharynx; onset September 1909, during 5th wk. of 4th pregnancy; had *U.R.I. for 2 wks. prior to 1st operation*; March 3, 1910, ethmoid cells curetted, sphenoid sinus opened, *contained pus, was curetted, right superior maxilla removed*; Coley toxins (Tracy XI) begun 7 days later, 14 i.m. in 21 days, very small doses; only 1 reaction; confinement May 1910, became pregnant without any menses, 2 mos. later; immediate recurrence; 2 more operations August and September 1910; 5th child born April 3, 1911; considerable dull pain right side of face; May 11, 1911, 4th operation attempted, abandoned as disease extended to left side of face, nose, would have required excision of left superior maxilla as well, toxins resumed, given in vicinity of tumor, *febrile reactions to 103° F for 3 wks., recurrent tumor completely disappeared*; developed *pulmonary tuberculosis* but recovered after being in sanatorium; 6th child born March 1914; (total of 9 children, 6 born after onset) no further evidence of disease; in good health until cholecystitis, 1942, 1944; operation advised for single large calculus, not done; 1950 chronic bronchiectasis; emphysema, generalized arteriosclerosis, arthritis, bad fall, 1954, lung symptoms then subsided; hypertension, *recurrent pneumonia* 1957; some evidence renal neoplasm August 1957; death November 5, 1957, 48 years after onset of sarcoma. (313, Case 5; 314, Case 1; 583; 589)

25. (Craver): Male adult; Hodgkin's disease; onset 1926; also had *advanced pulmonary tuberculosis, with cavity formation and positive sputum*, when admitted to Memorial; Survived 14 yrs. after onset. (166; 528)

26. (Coley): S.B., male, aged 49; inoperable carcinoma thyroid, *quiescent 5-6 yrs. during active phase pulmonary tuberculosis; metastases to clavicle developed as lung condition was "approaching arrest"*; radiation; disease not controlled, death October 1930, about 8 yrs. after onset. (589)

Syphilis: 1 Case

27. (Auzias-Turenne): Female, aged 30; thrice recurrent carcinoma breast, axillary metastases; (had 3 operations); general health alarming; further surgery not possible,

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patient told of hopeless prognosis, "drowned her sorrows in debauchery" and thus developed *syphilis, complete disappearance of cancer*; later given mercurial treatment for syphilis; no further recurrence several yrs. later, mammary region dry and firm. (Note: As a result of this case Auzias-Turenne inoculated syphilis in several cases of cancer. Didot (1851-1852) described these experiments and his own views as to the antagonism of syphilis and cancer). (201)

Cholera, Typhoid, "Ptomaine," Dysentery, Diarrhea or Colitis: 11 Cases

28. (Delens): Male, aged 55; lymphadenoma both orbits, disease generalized; developed *cholera*; during convalescence also had a "cutaneous eruption resembling rubeola" and *suppurating otitis media*; the tumors began to decrease in size from onset of cholera, regression continued until all had disappeared without trace; end result unknown. (194; 200)

29. (DeWitt): Female adult; spindle cell sarcoma parotid; partial removal, inoculation erysipelas cultures, remains of growth entirely disappeared but recurred in 1 yr.; erysipelas toxins then injected; growth again completely disappeared; later another recurrence disappeared after an attack of typhoid; patient died 5 yrs. later from sarcomatosis. (123; 147; 198)

30. (Neumann): Male, aged 50; extensive lymphosarcoma involving cervical nodes, especially on right side, concurrent typhoid lasting 8 wks.; complete disappearance of all tumor masses; not traced. (588)

31. (Hill): Female, aged 60; extensive hard intra-abdominal growth, patient had a severe attack of *ptomaine poisoning following which the growth disappeared*; there was no recurrence when last seen a year later. (327)

32. (Sen): Male, aged 50; inoperable gastric cancer; extensive perforation occurred while patient was having a "hectic fever"; free escape food through gastric and abdominal wall; pulmonary symptoms, cachectic; later dysentery; slight improvement (?); escape of food through ulcer somewhat diminished thereafter; condition steadily declined; not traced. (2; 780)

33. (Coley): G.A., female, aged 59; papillary cystadenoma primary in left ovary, removed at 1st operation, 1914; recurrence; subtotal hysterectomy, bilateral salpingo-oophorectomy, May 31, 1916 (W.J. Mayo); recurrence 1925, mass in umbilical region, ascites; 3rd operation (Mayo) June 4, 1925, secondary papillary peritonitis found, cysts on peritoneum, omentum, and abdominal wall, also many floating myxomatous bodies, incomplete removal; clinically malignant; x-ray therapy June 16-27, 1925; disease not controlled; Coley toxins begun January 15, 1926; marked reactions, remarkable improvement, abdomen diminished 7½ cm.; general condition improved patient up & about; March 15, 1926 developed severe colitis (15-20 stools daily), fever 104.5° F. for

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7 days; prostrated, abdomen steadily and enlarged rapidly (gas, fluid, tumor), condition critical; spontaneous opening formed, drained 2-3 quarts necrotic tumor and fluid 1st day, several pints daily for next 10 days; complete disappearance abdominal growth; regained health; recurrence 1927, no further treatment; death September 1927, 11 yrs. after onset. (123; 583j; 589)

34. (*Fèvre*): Male infant; sympathicoblastoma, with multiple superficial metastatic lesions; child born prematurely at 8 mos.; attack of diarrhea at 4 mos. (diaper rash?); metastatic tumor at corner of right eye 1st noted about that time; then explosive development of multiple tumors on plantar surface feet, right groin, buttocks, scrotum, back, left side, thorax and inner canthus left eye. Only 1 other tumor developed later on scalp; tumor near right eye removed for biopsy; principle tumor mass deeply embedded in right scrotum, no perceptible tumor in lumbar or abdominal region, though left lobe of liver was a little larger; no treatment given other than vitamins; prognosis grave; complete regression all tumors in next 2-3 mos.; alive and well December 1957, 22 yrs. after onset, not traced thereafter. (249; 259)

35. (*Ochsner Clinic*): M.B., female infant; inoperable neuroblastoma, present at birth, generalized; born at full term, February 2, 1950, weight 6 lbs.; abdomen abnormally large at birth; breast fed 2 mos. during which time mother and other children had influenza, not severely; (during the flu infection breast became swollen, almost abscessed, but she continued to nurse the baby); child seemed well during 1st mo., but local M.D. gave 4 injections vitamin K as her blood did not coagulate properly; at 2 mos. metastatic masses began to appear in groin, over pubes, lower abdomen, chest, back and head; large mass, apparently liver extending from costal margin to below iliac crest, well beyond midline; child pale, appeared chronically ill, biopsy May 29, 1950; developed diarrhea, while in hospital, causing severe diaper rash, slight fever; June 1, 1950 nitrogen mustard given i.v. for 4 days, also blood transfusion; discharged; prognosis hopeless; condition much worse; 2 wks. later developed U.R.I., given penicillin gradually began to improve; at 8 mos., weight 18 lbs., liver had receded, only 2 or 3 subcutaneous nodules remained, blood normal; at 2 yrs. developed furunculosis, continued to do well; April 1951, 3 remaining subcutaneous nodules excised from lt. thigh, groin, again reported as neuroblastoma; 2nd course HN₂ i.v. for 4 days, then after 3 days rest 4 more; each time this was given developed "runny nose," given further penicillin; by October 1951 liver no longer palpable, all evidence of disease had disappeared, complete skeletal survey negative, except for mottled calcification in region of liver; November 26, 1951 mass in rt. quadriceps excised, reported as neuroblastoma with differentiation toward ganglioneuroma; penicillin for 1 mo., severe allergic reaction, entire body covered by red rash, eyes swollen shut; 2 more cycles nitrogen mustard December 1951, January 1952; at age of 3 developed varicella; at 4 or 5, rubeola; no further evidence of disease, grew normally in every way; married, had a child in 1976, in excellent health, 1979, 29½ years after onset. (259; 589)

36. (*Roussy*): Male, aged 22; inoperable sympathicoblastoma primary in right iliac

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fossa and hypochondrium size fetal head; June 1937: *attack enteritis*; mass 1st noted at this time; biopsied, pronounced typical sympatheticoblastoma; given x-ray therapy 1 mo.; another mass developed on left side, severe constipation, loss of weight; August 7, 1939: operated, primary mass dissected free, secondary mass involving mesocolon could not be removed; tumor examined; *no mitoses, sympatheticoblasts had about disappeared*, being replaced by ganglion cells (tumor in transition between sympatheticoblastoma and ganglioneuroma); another course x-ray (4,000 r); *concurrent pneumonia or pneumonitis*; recurrent indurated area along abdominal incision and underlying mass in pelvis pressed on bladder and rectum; *acute cystitis with hematuria* for several mos., ending early April 1940; *indurated area along scar and underlying recurrent mass entirely disappeared during this prolonged infection*; however, metastases developed with neurological symptoms; lesions in D5 vertebra, ramus lower jaw, cervical region, rib, epigastric region, x-ray therapy given; symptoms rapidly growing cerebral metastasis (cephalagia, edema of eyelids, exophthalmos); these cleared up completely without any therapy following *epistaxis*; these phenomena recurred several times, of longer or shorter duration, sometimes on right, sometimes on left, each time disappearing after an epistaxis of the homologous naris; patient alive January 1, 1941, with further metastases to ribs, 4 yrs. after onset, end result unknown. (259; 740)

37. (Pack): G. McC., male infant, aged 2 mos.; spindle cell sarcoma left thigh ("fibrosarcoma, Grade III"); onset soon after birth; tumor of rapid growth, involved all quadriceps muscle when excised January 24, 1938; x-ray treatment, immediately developed *diarrhea, so x-ray stopped after 1 treatment; then had acute bronchitis, to 103°F., dehydrated*; given saline subcutaneously; x-rays revealed circular shadow in mid-portion right lung; x-ray therapy to thigh 2400 r skin dose; transfusion; further *diarrhea, irritation of skin, intergluteal fold, papules on face; chest lesion cleared up; no recurrence or metastases*; alive and in perfect health, 1960 22 yrs. after onset. (528; 583i; 589)

38. (Patrizio): Female, aged 55; adenocarcinoma rectum at junction of sigmoid; onset, September 1951, *recurrent episodes diarrhea, bleeding, colic, occasional chills, slight fever; slight tenderness across lower abdomen*; February 1952: stool cultures positive for *Salmonella barielly*, antibiotics (sulfasuxidine, chloromycetin); stool remained positive except for 2 mo. period; hospitalized June 1952, barium studies, biopsy, abdominoperineal resection distal sigmoid and rectum; *complete recovery*, no further evidence of dysentery infection or cancer; alive and well 1980, over 28 yrs. after onset. (258; 589; 633)

Diphtheria: 1 Case

39. (Hoffman): Male adult; papillary adenocarcinoma cardiac end of stomach, far-advanced, growth size of orange; *disappeared completely following attack of diphtheria*; given diphtheria antitoxin; growth recurred to former size; *again disappeared completely following 2nd attack diphtheria*; again, recurred to former size; patient then had

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erysipelas; growth shrank two-thirds, then again increased; no radiation or surgery used; disease progressed, death 1930. (528; 589)

The following 18 cases had concurrent viral infections:

40. (*Beadles*): A.G., female, 55; rapidly growing adenocarcinoma right breast, axillary, supraclavicular metastases; (also had concurrent spindle cell sarcoma iliac region 33 yrs. duration, repeated recurrence, many operations); *onset of breast cancer occurred immediately after influenza*, (applied mustard poultice to chest); ulceration soon occurred; radical mastectomy; end result unknown. (24)

41. (*Knight*): Female, aged 45; inoperable cancer liver; *concurrent influenza, very ill, condition grave, from then on liver shrank, patient recovered*; 18 mos. later recurrence, eventual death. (91)

42. (*Thomas*): Male adult; far advanced cancer mouth, death seemed imminent; then developed *severe gripe*, confined to bed several days; considerable decrease in size and healing of tumor occurred; *growth entirely disappeared in a few weeks*; no recurrence, he died of another intercurrent condition subsequently. (462, p. 264)

43. (*Rubens Duval*): Mme. M., female, aged 47; inoperable infiltrating adenocarcinoma of stomach arising in area of hypertrophic gastritis; incomplete removal by partial gastrectomy, November 20, 1930; extracts from gastric adenocarcinoma and from case of hypertrophic gastritis then given orally for 9½ mos.; condition improved, gained weight, resumed normal activities; 4½ mos. after cessation of treatment, epiploical metastases, ascites present, oral therapy resumed; general condition remained good but peritoneal metastases increased; however, appetite and general condition remained good until February 1933, then developed *gripe, which caused "most grievous effect on the evolution of the cancer"*; *abdomen greatly increased in size (ascites), edema lower extremities, abdominal wall*; then given renal and splenic extracts and other medication; right pleural effusion, requiring thoracentesis, very weak; by May 1933 considerable improvement; tumor extracts continued orally; end result unknown. (752)

44. (*Wendel*): Female, aged 6; inoperable extensive retroperitoneal sympatheticoblastoma; onset December 1934; became pale, apathetic, tired, *developed gripe, parotiditis; tumor noted following these infections*, pain 1st noted March 31, 1935; obstruction developed requiring exploration, extensive hard nodular mass totally inoperable, so only biopsy taken; symptoms of obstruction ceased after operation; given 2 courses x-ray; temporary regression (slight); then increase in size, pressure on spinal nerves, cord bladder; frequent catheterization, *cystitis, pyelitis*; death August 27, 1935, 8 mos. after onset; *no evidence of metastases at any time*. (713; 823)

45. (*Beck & Howard*): W.A., male infant; apparently inoperable neuroblastoma left adrenal, occasional vomiting at 3 wks.; September 1944, mass felt 2 cm. below costal

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margin, liver enlarged; *concurrent comedos, acne, considered due to stimulation of sex hormones*; biopsy at 9 wks.; x-ray, 20 in 38 days, 1400 r tumor dose in upper abdomen; 2 mos. later 16 in 20 days (1250 r); skin in good condition; acne disappeared after radiation ceased; small mass still felt in L.U.Q.; *concurrent influenza, November 1945, gradual complete regression*, except for small palpable mass and slight displacement of left kidney; 3rd cycle of x-ray (13 in 16 days, 1400 r tumor dose); *another respiratory infection, October 1949; few days abdominal pain, vomiting March 1950; right otitis media, tonsillitis*, January 1951; no further evidence neuroblastoma; in good health except for some dwarfing due to radiation: (interfered with formation of spinal bodies) also radiation nephritis (blood urea nitrogen rose to 80 if he didn't drink adequate fluids); 1963, somewhat of psychological problem, not working; overdose of Miltown, requiring hospitalization; complained of pain, weakness of legs, possibly due to radiation effects; he was married in early January 1968, died uremia, pulmonary edema, February 6, 1968, a month later, 34 years after onset. (26; 259; 589)

46. (Greenough & W.B. Coley): Mrs. J.C.S.W., adult; carcinoma breast; radium, x-ray given by Coley; condition satisfactory until January 1935 when *acute grippe with bronchitis developed; immediate reactivation of carcinoma; breast became suddenly very much enlarged, diffusely indurated, also reddish indurated areas on skin over breast toward axilla, skin adherent, number of skin nodules of irregular shape seen; also large mass of nodes in left axilla, and questionable thickening above clavicle*; chest films showed considerable diffuse fibrosis in lungs; further x-ray by Greenough; disease progressed, death August, 1935, over 3 years after onset, 7 mos. after reactivation occurred. (123)

47. (Moffat): D.B., female, aged 14; inoperable lymphosarcoma cervical, supraclavicular and inguinal nodes, onset, fall of 1912; parotid gland enlarged to size of small egg anterior to ear; under course of hot baths it diminished in size, *disappeared following measles*, fall of 1913; *series of colds*, 1914; appendectomy May 1915; December 1915, *left tonsils and parotid began to enlarge during a cold, following diphtheria*; Christmas 1915, cervical lymph nodes enlarged (bilateral); February 1916, *acute inflammatory rheumatism, all joints in turn, severe endocarditis*, resulting in serious cardiac dilation, mitral insufficiency, biopsy June 1916; Coley toxins begun June 1916 (Tracy XI), given every 3rd or 4th day i.m. all in thigh, near groin, mostly left side; no apparent benefit until after 1st marked reaction July 10, 1916 (102.1 °F.); thereafter the more severe the reaction the more marked reduction in size occurred; slow steady regression; radium treatment, causing burns, August 1916; regression more marked for awhile, then slower; 2nd radium November 1916; toxins continued, brief intervals of rest; 3rd radium July 17, 1917; general condition, including heart, very much improved; toxins given 3 yrs.; disease controlled, then death August 20, 1920, 8 yrs. after onset. (80; 123; 307)

48. (Peacock): Adolescent male; inoperable tumor in maxilla; developed concurrent infection believed to be *measles with fever; complete regression, no further evidence of*

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disease; employed as laboratory boy thereafter; no recurrence; traced well several yrs. (589)

49. (Riffel): Age, sex, not given; carcinoma of face; developed *smallpox, causing complete regression and apparent cure*; end result unknown. (704)

50. (Green): Female, aged 4½ yrs.; inoperable retinoblastoma recurrent in the parotid region after enucleation of the eye; *temporary regression during an attack of mumps*; the disease recurred 2 wks. later; end result unknown. (123)

51. (Van Creveld & Van Dam): Female, infant, inoperable sympatheticoblastoma, apparent from birth May 1938; *developed varicella at 1; wbc 9,600*; 3 x-ray treatments cause no diminution; exploration; tumor incised for biopsy causing hemorrhage, difficult to control; no other treatment; gained weight and grew naturally, *tumor slowly regressed during next few years.*; patient married in 1960; daughter born 1963; in excellent health 1970, 32½ yrs. after onset. (259; 889)

52. (London): F.H., female, aged 39; inoperable multiple myeloma; onset February 1949; ACTH given for 25 days, also 4,500 cc. whole blood without benefit; urethane given for 4 mos., repeated transfusions; disease progressed despite therapy; *serum hepatitis, very ill; spectacular and complete remission all symptoms of myeloma, gained 25 lbs.; blood, urine tests all normal for over 2 yrs.*, then symptoms recurred, causing death, over 4 yrs. after onset. (468)

53. (Ellison): R.M., male, aged 59; recurrent adenocarcinoma rectum with metastases to peritoneum and mesentery; onset August 1952; resection January 1953; recurrence few mos. later; peritoneal metastases present, especially along left pelvic brim and over sacrum; large nodes present in base of mesentery; 2nd operation July 1953 for removal of these nodules; *virus pneumonia February 1954, with fever for 2 wks.*; barium enema given for routine follow-up exam, caused perforation of colon requiring emergency operation August 11, 1955, no evidence tumor found clinically or histologically; well next 2 yrs. then began tiring easily, urinary symptoms (non-functioning left kidney); large metastatic tumors found at nephrostomy, involving urinary bladder; palliative x-ray (5800 r) for excruciating back pain; death November 26, 1958, over 6 yrs. after onset. (237; 589)

54. (Hilton): Female, aged 56 at time of infection; carcinoma of right breast, skeletal and lymph node metastases; radical mastectomy 18 mos. after onset; well 2 yrs., then several osteolytic metastases to femora, left ilium; no treatment given as pain ceased 2 wks. after x-ray examination; well 3 yrs. then right axillary metastasis; given x-ray, regressed; again well 3 yrs. then metastases to right supraclavicular triangle; responded well to radiation; 2 more appeared 1 yr. later, also regressed after x-ray; during these 7 yrs. after skeletal metastases 1st appeared, general health remained good, patient pain-free, led normal life; 11½ yrs. after onset: *acute febrile illness during influenza*

SERIES B: NON-PYOGENIC

epidemic; general condition then deteriorated, low back pain recurred, multiple skin metastases in mastectomy area; extension of metastases in pelvis; x-ray to skin lesions; temporary response; death from very widespread metastases. Compare with Case 45 above, in which a quiescent breast cancer was reactivated immediately after grippe. (328)

55. (*Delor*): Mrs. H. P., female, aged 45; operable adenocarcinoma of colon, adherent to ovaries, uterus; (5 cases gastric or colon cancer in paternal family history); onset, October 1956, intermittent lower abdominal cramps, constipation; stools normal, no blood, mucus; symptoms worse during menses; 13 mos. after onset *severe sore throat, septic temperature to 103° F.*, marked cervical, also some axillary and inguinal adenopathy; no masses noted in abdomen; next 5 mos. continued to have bouts of abdominal cramps intermittently; throat cultures negative; sigmoidoscopy negative (3 times); explored May 1957 wall of bowel firmly adherent to ovaries, uterus, (15 cm. involved); resection, side-to-side anastomosis, bilateral oophorectomy, total hysterectomy performed; regional lymph nodes negative—*showed lymphoid hyperplasia; postoperative exacerbation of febrile adenopathy; diagnosed as cat scratch fever by viral lab; fever lasted 4 wks.; then asymptomatic*; no recurrence or metastases, in good health 1976, 20 yrs. after onset. (195; 258)

56. (*Bowden and Murphy*): M.O., female, 61; numerous metastatic leiomyosarcoma, primary in stomach and colon, involving lt. lobe liver; onset, late 1945 or early 1946; resected June 1946; well 6½ yrs. until December 1952, then weakness, nausea, episodic vomiting, epigastric mass; lost 10 lbs. in 6 mos.; rt. hepatic lobectomy May 26, 1953, metastatic masses, 3.5–17 cm. in diameter in resected specimen; 4 transfusions prior to, 9 during operation; *low grade subphrenic abscess postoperatively, septic for about 2 wks., then homologous serum hepatitis; complete recovery*; no further evidence disease, 18 mos. after surgery, over 8 yrs after onset. (58)

57. (*Chardot*): M.H., male, aged 62; very undifferentiated epithelioma of lt. upper lobe bronchus; radiation (factors not recorded); pneumonectomy; 10 mos. later marked decrease in general health, *severe icterus*, hepatomegaly, all symptoms at first attributed to liver metastases, but were due to *viral hepatitis* (had received transfusions preoperatively), prognosis grave; *N.E.D. until death other causes over 6 yrs. after onset.* (103)

58. (*Bell*): J.M., male, aged 37; inoperable poorly differentiated epidermoid carcinoma, grade 3, of much of upper lobe of right lung, extensive metastases to pleural space; heavy smoker for 20 years; onset, August 1958, exertional dyspnea, progressively worse next 6 mos., lt. subscapular pain; early February 1959, *chill, pleural effusion, pneumonia*; admitted February 27, 1959; *WBC 23,600*; large tumor masses in lt. upper thorax; scalene fat pad biopsied; "hyperplastic lymph nodes"; 3 thoracenteses (1,600, 2,300, 700 ml. serosanguineous fluid, no tumor cells); March 11, 1959, exploratory thoracotomy: extensive involvement left pleural space—lesions 1-3 cm. in diameter,

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visceral and parietal surfaces; bulk of upper lobe firmly consolidated; *fever 100°-103° F. for most of 2 wks.* after surgery during palliative x-ray therapy (1,200 r tumor dose); after discharge, he showed very positive attitude toward survival, self imposed hyperalimentation, healthy life style gained 40 lbs., *complete regression of primary and metastases*; N.E.D. 5½ mos. later and again over 10 yrs. later. (30a; 30b)

SERIES C, PYOGENIC INFECTIONS OCCURRING SPONTANEOUSLY IN OPERABLE CANCER

This series comprises a total of 117 cases of operable cancer in which a pyogenic infection developed. In 19 of these the patients were untreated except for biopsy. In the remaining 98 infection occurred before or after surgical removal. In 17 of these cases Coley toxin therapy was also administered (Groups 4 and 5). In all but a few of these 117 cases the diagnosis was confirmed by microscopic examination. The cases have been grouped as follows:

Group 1, Successes, Infection alone, microscopically proven, traced 5 to 54 years after onset: 61 cases.

Groups 2, Indeterminate, Infection alone, traced less than 5 years: 27 cases.

Group 3, Failures, Infection alone: 11 cases.

Group 4, Successes, Infection and Toxin Therapy: 8 cases.

Group 5, Failures, Infection and Toxin Therapy: 10 cases.

Instead of brief abstracts the cases in series C are listed in tables, to facilitate analysis.

5 SERIES OF TABLES FOLLOW

SERIES C, GROUP 1, SUCCESSES: OPERABLE CANCER IN PATIENTS IN WHOM PYOGENIC INFECTION DEVELOPED SPONTANEOUSLY: 61 CASES

Physician References	Sex, Age & Date	Histologic Type, Site & Extent of Tumor	Surgery or other Therapy	Type of Infection Duration & Extent	Final Result Years Traced After Onset
1. Mott 80; 136; 144; 565	male 19 1828	osteosarcoma clavicle size of 2 fists, fungating	total excision clavicle (first ever performed)	suppuration in wound	N.E.D.; died other causes 54 yrs. later
2. Freund 268; 566; 857; 583J	female 37 1876	ulcerated carcinoma cervix 2nd nodule in fundus	hysterectomy, left ovariectomy	pre- and postoperative spiking temperature; extensive pelvic abscess with fistulae	wound healed in 4 wks.; N.E.D., traced well 20 yrs.
3. Pozzi 678; 679; 680; 583J	female 25 1878	bilateral malignant ovarian papilloma (left size of full term pregnancy, rt. half as large); extensive ascites	bilateral oophorectomy, difficult operation	postoperative intraperitoneal injections iodine 100 & 150 gr. each; caused peritonitis each time; postoperative fever to 39.8° C. for 2 wks.; suppuration in vagina & suprapubic sinus, abscess evacuated; infection lasted 4 wks.	complete recovery; well, N.E.D. for 20 yrs.; then ascites returned, 2nd operation, 1899; recurrent tumor fixed to pelvic floor; no attempt at removal, ascites & edema disappeared, well another yr., death 1901, 25 yrs. after onset
4. Gross 949	male adult 1879	osteosarcoma femur	amputation	wound suppurred freely	no recurrence or metastases; traced well 5 yrs.
5. Bull 124, p. 214; 135, p. 8	male 35 1888	osteosarcoma femur involving distal third	amputation	septic infection of stump; high fever, multiple abscesses	no recurrence or metastases; traced well 5 yrs.
6. Czerny 129; p. 18; 172; 583K; 717, p. 218	female adult 1886	mammary carcinoma, recurrent 1 yr. after radical mastectomy numerous hard subcutaneous nodules	at 2nd operation involved skin & fatty tissue removed	moderately severe erysipelas in region of wound following 2nd operation	no further recurrence or metastases; traced well 20 yrs.

7. McCosh 484	male 33 1891	recurrent retroperitoneal sarcoma, primary size of cocoanut removed 2 yrs. previously	2nd very extensive operation, wound left partially open	wound suppurated freely for 3 mos.; sinus then healed; gained 40 lbs.	no further recurrence; in perfect health, traced well 12 yrs.
8. Coley 130; 583K	female adult 1881	mammary carcinoma	mastectomy	erysipelas during wound healing	no recurrence or metastases; traced well 15 yrs.
9. Coley 130; 583K	female adult 1891	mammary carcinoma	mastectomy	erysipelas during wound healing	no recurrence or metastases; traced well 5 yrs.
10. Coley 130; 583K	female adult 1891	mammary carcinoma	mastectomy	erysipelas during wound healing	no recurrence or metastases; well 5 yrs.
11. DeGaetano 188; 344; 718	female 56 1892	epithelioma forehead 2 yrs. duration	untreated prior to 1st erysipelas; further excision; plastic operation	1892; facial erysipelas over tumor area, high fever over 10 days; primary gradually disappeared; healed completely; 1896: 2 more attacks erysipelas (mild), no effect on recurrent ulceration; 4th erysipelas 14 days after plastic operation, moderately severe	well 4 yrs., then fell on head; former tumor site again ulcerated; no further recurrence after final erysipelas, traced well 12 yrs. after onset
12. Lewers 450 p. 14; 583J	female 55 1895	squamous cell epithelioma, papillary type; large cauliflower growth of cervix	vaginal hysterectomy; operative field inundated with fetid pus	preoperative fever & infection of body of uterus	no recurrence or metastases; traced well 5 yrs.
13. Rovsing 344; 744; 838	sex? age? 1895	osteosarcoma of scapula	excision	postoperative erysipelas	N.E.D. 17 yrs. then recurred, not traced subsequently
14. Neale 123; 307	male 28 1897	lymphosarcoma of neck	excision	extensive suppuration in wound	N.E.D. thereafter; traced well 8 yrs.

SERIES C, GROUP 1, SUCCESSES: OPERABLE CANCER IN PATIENTS IN WHOM PYOGENIC INFECTION DEVELOPED SPONTANEOUSLY

Physician References	Sex, Age & Date	Histologic Type, Site & Extent of Tumor	Surgery or other Therapy	Type of Infection Duration & Extent	Final Result Years Traced After Onset
15. Boomer 123; 583K; 137, p. 120	female adult 1897	extensive carcinoma both breasts	involved area excised	severe erysipelas during wound healing	N.E.D. thereafter; traced well 7 yrs.
16. Müller 344; 355; 569; 844	female 1½ 1898	myxosarcoma (about 8 cm.) femur or fascia of thigh	exploratory incision (biopsy); amputation advised but refused	pyocyanous wound infection, profuse drainage for 4 wks., moderate fever for 3 wks.	complete regression; no recurrence or metastases; well 1921, 23 yrs. after onset
17. Neale 123; 583K	female 36 1899	spindle cell sarcoma breast	mastectomy	erysipelas during wound healing	N.E.D. thereafter; traced well 5½ yrs.
18. Grey Turner 299; 583K	female 47 1907	carcinoma left breast; axillary metastases	radical mastectomy	empyema left side	no recurrence or further metastases; alive & well 18 yrs. later
19. Jackson 352; 545	male 35 1909	obstructive, very cellular endothelioma of left bronchus	bronchoscopy; growth removed by successive snips of bronchoscopic tissue forceps	preoperative chronic inflammation & infection for nearly 5 yrs.; postoperative fever & suppuration	gained 26 lbs. in 9 mos.; no recurrence; alive & well 19 yrs. later
20. Elting 583K; 589	female 32 1914	extensive mammary carcinoma, widespread ulceration	radical mastectomy; several ribs resected	violent postoperative erysipelas infection	N.E.D.; traced well 30 yrs.
21. Grey Turner 258; 299	female adult 1915	typical restricting carcinoma of sigmoid causing obstruction, great distention; growth adherent to pelvic wall	caecostomy; 3 wks. later exploration; resection, left oophorectomy & salpingectomy, anastomosis not possible; left inguinal colostomy; abscess incised	abscess between appendix & growth	N.E.D.; perfect health 9 yrs., then hemiplegia due to vascular degeneration; traced well 10 yrs. after operation
22. Mayo Clinic 523; 583K; 589	female 48 1921	carcinoma (grade III) right breast; axillary metastases	radical mastectomy	postoperative staphylococcus infection; wound suppurated for 2 mos.	no recurrence or metastases; in good health except for later crippling arthritis; died June 1960, bladder carcinoma 39½ yrs. after onset, at 87 yrs.

23. Harris 57, Case 867	male 11 1921	osteogenic sarcoma scapula	scapulectomy	postoperative wound infection (hemolytic streptococcus & erysipelas)	N.E.D.; traced well 19½ yrs.
24. McKim 485	female 68 1921	fibrosarcoma knee, very cellular growth 1st operation January 1921, excision primary & femoral metastases; 2nd operation 7 mos. later for 2nd larger recurrence, intolerable pain	amputation for very extensive bleeding, ulcerated recurrence; tissue very edematous at amputation site	prolonged very severe streptococcal infection; no healing for wks., then rapid healing	no further recurrence or metastases; died other causes at 89, 21 yrs. after infection
25. Orton 548; 618	male 29 1922	fully malignant, quite diffuse carcinoma bronchus	bronchoscopy; lesion removed through bronchoscope	pt. insisted on injections of autogenous vaccine for 8 wks.; "pus" in trachea & bronchus; postoperative pneumonia or lung abscess	N.E.D.; well 15 yrs. after onset
26. Liek 454; 727	male 52 1923	advanced carcinoma penis; bilateral groin metastases	amputation penis; radical groin dissection; some x-ray therapy	erysipelas; 40 recurring attacks in region of wounds at 3-6 wks. intervals, lasting 4-6 days; sharp rise in temperature	N.E.D.; traced well 5 yrs. after onset
27. Memorial Hospital 528; 589; 583C	male 25 1925	recurrent giant cell tumor femur (onset 1920) path. fracture; long period of disability (over 5 yrs.)	explored; curetted for biopsy; radium packs 151,154 mch. in 8 mos.	decubitus ulcer on heel; diathermy burn (8 cm.); 1925; erysipelas in burned area, spread to groin, high fever	no further evidence activity after erysipelas; returned to work; 30 yrs. after, hypertension, arthritis; 1974, lung cancer; metastasized causing death July 19, 1974 54 yrs. after onset
28. Mayo Clinic 523; 589	female 11 1926	osteogenic sarcoma proximal ½ rt. humerus; pathologic fracture 1924	incisional biopsy, x-ray 7000r tumor dose (13,500r skin does to 7 areas) complete regression; fracture healed	few mos. after recovery, scarlet fever; later series of styes on eyelids; middle ear & U.R.I. acute appendicitis 1947; bacterial endocarditis 1963	N.E.D. except for radiation changes in shoulder girdle (bones, muscles, skin); X-ray cancers in irradiated skin; 1976, cancer rt. breast; mastectomy; it metastasized; had pacemaker; died radiation fibrosis, myocarditis, 1978, 52 yrs. after infections

SERIES C, GROUP 1, SUCCESSES: OPERABLE CANCER IN PATIENTS IN WHOM PYOGENIC INFECTION DEVELOPED SPONTANEOUSLY

Physician References	Sex, Age & Date	Histologic Type, Site & Extent of Tumor	Surgery or other Therapy	Type of Infection Duration & Extent	Final Result Years Traced After Onset
29. Crump 123; 589	male 50 1929	epithelioma lip; extensive involvement nodes	excision of primary & involved nodes	severe erysipelas shortly after leaving hospital	N.E.D.; traced well 9 yrs. after onset
30. Memorial Hospital 528; 589	male 4½ 1929	lymphosarcoma rt. anterior cervical nodes	surgical removal	fever; wound infection; 2 yrs. later, otitis media; mastoidectomy	N.E.D.; well 1977, 48 years after onset
31. Martin 561; 589	female 53 1930	ulcerated basal cell carcinoma cheek	biopsy; untreated	severe facial erysipelas from biopsy wound (lasted 2 wks.)	complete regression, no recurrence; well over 5 yrs.
32. Dunphy 215; 258	male 58 1930	adenocarcinoma cecum extending beyond bowel, invading abdominal wall in region appendectomy scar	incision, drainage of abscess; 2 wks. later rt. colectomy, end-to-side ileotransverse colostomy	large abscess appeared in region appendectomy scar 6 wks. after onset of ca. symptoms (diarrhea, anorexia)	well over 2 yrs., then large recurrence involving abdominal wall; round ligament of liver; excised en bloc (of slow growth histologically); well, N.E.D. 1939, over 9 yrs. after onset
33. Graham 292; 293; 589	male 48 1933	squamous cell carcinoma lt. upper lobe bronchus	total pneumonectomy (first ever performed successfully)	empyema on 9th postoperative day; coughed up pus, drainage re-established	N.E.D.; resumed active practice obstetrics; very well until hip fracture 1961; then hypertension, arteriosclerosis; death 1964, 30 yrs. after onset; hypertensive, cardiovascular & renal disease; no cancer seen at autopsy
34. Lavedan 431; 589	female 49 1934	ulcerated epidermoid carcinoma of ear, 10 mos. duration	incisional biopsy; untreated	erysipelas near tumor fever to 40.6°C; spread over face, ears, part of neck; lasted 2 wks.	complete disappearance well & free from recurrence over 22 yrs., died other causes
35. Memorial Hospital 528; 583C	female 26 1936	rather cellular giant cell tumor lt. fibula, not entirely benign; pt. obese, 240 lbs.	1936, curettage; 1937, resection of fibula for extensive recurrence	1936; postoperative fever; wound incised, much thick grey discharge; 3 furuncles on leg that yr., 1937, postoperative fever (103.6°F.); wound infected over 2 mos.	complete healing 6 mos. after resection of fibula; no further recurrence; married, last traced well 1950, over 14 yrs. after onset

36. Memorial Hospital 528	female 35 1936	extensive liposarcoma rt. thigh, 14 x 6 cm.	explored, no attempt at removal; radium needles inserted; x-ray daily for 18 days no effect; radium packs (52,000mch.); regressed 1/3; excision, skin grafting	pyocyanous infection of ulcerated tumor; earache; postoperative erysipelas infections leg, thigh	no recurrence; developed severe lymphedema; 4 Kondolean operations; finally limb amputated, 1962; N.E.D., well except for severe phantom limb pain, November 1963, over 27 years after onset
37. Dunphy 215; 258	male 52 1939	rapidly growing adenocarcinoma sigmoid, involving bladder, terminal ileum	July 1939, 18 mos. after onset rt. transverse colostomy, 3 wks. later resection sigmoid, terminal ileum, upper 1/3 urinary bladder; colostomy closed in 3 wks.	wound infection following colostomy, 3 wks. prior to resection	2 yrs. later recurrence in L.L.Q. involving sigmoid, mesentery, bladder, lt. ureter, retroperitoneal tissues, many lymph nodes; resected with difficulty; permanent colostomy; N.E.D., alive well 1946, 8 yrs. after onset
38. Lavedan 431; 589	female 72 1939	ulcerated epidermoid epithelioma temporal region of 7 mos. duration	biopsy, untreated	facial erysipelas, also bronchitis, fever to 40.5°C.; extreme prostration, delirium; (effect on tumor not evident for 2 mos.)	then complete regression & healing in 6 wks., no recurrence or metastases; death following cerebrovascular accident 14 yrs. after onset
39. Morton 257; 559	female 40 1941	metastatic malignant melanoma, axilla, neck, primary on chest wall	primary, many metastatic lesions, excised; x-ray 1941	wound infection with drainage, 1941; cellulitis, 1943	no further metastases after 1941 infection; apparently well until death, cerebral hemorrhage, pulmonary emboli, 1959, 25 yrs. after onset, N.E.D. at autopsy
40. Livermore 459; 583A	female 37 1941	Wilm's tumor rt. kidney (extensive)	exploratory operation Wilm's tumor biopsied; abscess drained; x-ray (4100 r) started after 5 mos. suppuration, satisfactory response nephrectomy 6 wks. after x-ray	fever without chills due to perirenal abscess, also increase in renal colic (prior to exploratory operation); mucopurulent discharge for 5 mos. after it; chronic cystitis	gained 15 lbs. in 10 mos. after nephrectomy; excellent health thereafter; alive & well 1952, 14 yrs. after onset
41. Memorial Hospital 317; 528	male 17 1942	osteogenic sarcoma rt. femur	aspiration, incisional biopsies, prior to febrile episode, amputation after it	postoperative inflammation, fever (hemarthrosis) following biopsies; abscess on stump following amputation	N.E.D., in excellent health, married, 3 healthy children; last traced 1980, 38 yrs. after onset

SERIES C, GROUP 1, SUCCESSES: OPERABLE CANCER IN PATIENTS IN WHOM PYOGENIC INFECTION DEVELOPED SPONTANEOUSLY

Physician References	Sex, Age & Date	Histologic Type, Site & Extent of Tumor	Surgery or other Therapy	Type of Infection Duration & Extent	Final Result Years Traced After Onset
42. Memorial Hospital 528	female 61 1942	recurrent osteochondroma os innominatum with malignant degeneration, 15 x 8 x 9 cm.	excision, considerable blood loss, shock, transfusion 1200 cc. whole blood	very profuse suppuration, septic temperature for 2 wks.	N.E.D. 5½ yrs. after onset; then lost to followup
43. Memorial Hospital 528; 583H	male 12 1943	osteogenic sarcoma femur	amputation, 2 transfusions	septic temperature for 2 wks., cause unknown	N.E.D., in good health until death in auto accident 13½ yrs. after onset
44. Memorial Hospital 528	female 7 mos. 1944	Ewing's sarcoma femur possible mediastinal metastases	aspiration, incisional biopsies; x-ray 4200 r	6 febrile episodes, 1 before, the rest after radiation	N.E.D., in excellent health 1968, 25 yrs. after onset
45. Memorial Hospital 528, 583H	male 60 1945	chondrosarcoma ischium, pubis	hemipelvectomy, 5 transfusions	postoperative wound infection, febrile (to 103.4°F.)	N.E.D., in good health until 1926, then developed adenocarcinoma sigmoid, cholecystitis; Feb. 13, 1963, cholecystectomy; March 1, 1963, colostomy, Hartmann procedure for sigmoid ca; metastases from chondrosarcoma then noted in throat; death April 28, 1963 due to carcinoma, 19½ yrs. after onset of bone sarcoma
46. Sumner 257; 589; 847; 848	female 27 1946	primary malignant melanoma lt. ankle; later metastases rt. breast, lt. arm, lt. femoral region, abdominal wall, supraclavicular region, rt. eye; rapid growth during 3rd pregnancy, disseminated lesions during 4th pregnancy	untreated when infection occurred; many metastases excised, some incompletely; superficial femoral node dissection; fibrosis, chronic lymphadenitis, circumscribed malignant melanoma in nodes	primary tumor became infected, disappeared February 1946	metastasis over rt. eyebrow regressed spontaneously 1951; N.E.D. thereafter; skin over areas of former metastases depigmented; in good health next 15 yrs., last traced 1980, 34 yrs. after onset
47. Memorial Hospital 257; 528; 589	male 21 1946	malignant melanoma rt. ankle (10 cm.), twice recurrent, onset 1944	2 excisions; amputation; groin dissection	suppurating, fibrosing inflammation surrounding ulcerated lesion; postoperative drainage from groin wound	N.E.D. in excellent health 1979, 35 yrs. after onset

48. Memorial Hospital 528; 583H	female 48 1946	osteogenic sarcoma femur, principally osteochondromatous type; pathologic fracture; tumor 34 x 18 c.m.	hemipelvectomy 1946	chill, febrile (104°F.) 28 days postoperative, wound abscess; 200-300 cc. purulent matter evacuated, hemolytic Staphylococcus aureus; later influenza, fever 101.8°F.), further suppuration	N.E.D. able to do own housework, in very good health, excellent psychological adjustment; well 1980, 33 yrs. after onset
49. Memorial Hospital 528; 542B	male 54 1947	reticulum cell sarcoma tibia	x-ray; 1715 r tumor dose; amputation	chronic pyelonephritis prior to amputation; 6 mos. later virus pneumonia, febrile for 10 days (103°-105°F.) irrational	N.E.D. remained in excellent health working as an actor until sudden death, heart attack, September 6, 1960, 14 yrs. after onset
50. Memorial Hospital 257; 528	female 58 1947	subungual malignant melanoma great toe, metastases inguinal lymph nodes, labia	toe amputated, groin dissection	low grade infection of scars, cellulitis, inflammation, fever, erysipelas rt. thigh	no further metastases; well 9½ yrs., then adenocarcinoma pancreas, ampulla of Vater, subtotal pancreato-duodenectomy, cholecystectomy May 1955; disease progressed, death Oct. 17, 1955, over 10 yrs. after onset malignant melanoma
51. Memorial Hospital 528; 583H	female 42 1947	juxtacortical osteogenic sarcoma proximal femur	excision 1945; hip-joint disarticulation 1947	fever, wound infection following amputation, purulent drainage for 5 mos.	N.E.D. following infection; returned to work, using prothesis; very well 1980, over 33 yrs. after onset
52. Ward, et al 257; 582; 912a	male 52 1947	recurrent malignant melanoma concha lt. ear, metastases in lt. submaxillary lymph nodes	March 25, 1947; excisional biopsy; lesion extended to cartilage; recurred 5 mos. later metastases biopsied Feb. 1948; auricle amputated in continuity with lt. radical neck dissection (no tumor in specimen); Dec. 1948 gastroenterostomy for perforated duodenal ulcer; 1949-1952 biopsies on 3 occasions for suspicious nodules in lt. neck, posterior lt. neck & submental region, all negative	March 1948; fistula following radical surgery; responded to penicillin, local measures	N.E.D. in good health 1970, 23 yrs. after onset

SERIES C, GROUP 1, SUCCESSES: OPERABLE CANCER IN PATIENTS IN WHOM PYOGENIC INFECTION DEVELOPED SPONTANEOUSLY

Physician References	Sex, Age & Date	Histologic Type, Site & Extent of Tumor	Surgery or other Therapy	Type of Infection Duration & Extent	Final Result Years Traced After Onset
53. Memorial Hospital 529; 589	male 51 1949	epidermoid carcinoma rt. foot (plantar) possibly lt. foot in chronic severe radiation dermatitis (had received a great deal of x-ray also radium ointment to feet for fungus infections, 1938-1945)	mid-leg amputation, mixed vaccine injections (staph. strep.) 1948, 1960-62	hemolytic Staph. aureus infection rt. stump, fever 100°-102°F; hemorrhage from wound (400 cc.) mild shock	N.E.D.; obtained prostheses, resumed veterinary practice; 2 mild coronaries, 1956-1957; alive, well 1973, 25 yrs. after onset
54. Memorial Hospital 528; 583; 589	male 10½ 1948	osteogenic sarcoma distal lt. femur	high thigh amputation	postoperative inflammatory episode; slight throat infection; chronic otitis media 1950	N.E.D., obtained prosthesis, adjusted well, married, 1 child; excellent health 1980, 32 yrs. after onset
55. Monahan 531; 589	male 57 1950	extensive fibrosarcoma proximal lt. thigh 10 x 13 cm.	partial removal May 1960; 6 days later x-ray (1976r) agonizing pain, increase in growth followed; hemipelvectomy Aug. 1950 for pain relief	fever for 1 mo. after hemipelvectomy, considerable slough of skin with infection, draining sinus	N.E.D., returned to work part-time; died coronary thrombosis 1957, 7½ yrs. after onset, no evidence sarcoma at autopsy
56. Woodruff 573; 589	female 24 1951	Ewing's sarcoma distal lt. tibia, groin metastasis (sections reviewed at Lahey Clinic); became pregnant shortly after onset	incisional biopsy; x-ray to tibia; groin node biopsied May 1951, excised Nov. 1951; normal child delivered by Caesarian section at 28th wk.; x-ray then given to groin, chest	leukocytosis (12,000) prior to radiation; postradiation ulcerations; groin wounds suppurated	N.E.D., had 6 more healthy children, last one born 1966; in excellent health 1980, 29 yrs. after onset
57. Stone 258; 589; 836	female 60 1955	infiltrating adenocarcinoma sigmoid colon penetrating all layers of bowel	growth resected; end-to-end anastomosis; 6 implants of her tumor placed in subcutaneous fat of abdominal wall 7 days postoperatively at daily intervals	multiple staph. abscesses of buttocks & back postoperatively (none in sites of tumor implants)	N.E.D. in good health until 1962, then heart attack; died October 24, 1976, acute myocardial infarction, 21 yrs. after onset

58. Memorial Hospital 257; 528	male 41 1951	ulcerated, recurrent malignant melanoma rt. leg, metastases to rt. inguinal nodes	primary lesion removed by electrocautery; x-ray given monthly for 9 mos. 1 more March 1951; ulceration occurred May 1951; recurrence widely excised June 1951; skin grafts, rt. radical groin dissection July 1951	recurrence became ulcerated & infected, May 1951; bacitracin used; mild postoperative fever, much delayed wound healing, including donor area; furuncle, Oct. 1951, cleared up under aureomycin; infected sebaceous cyst in axilla, 1956	N.E.D., in good health working every day as a dentist, January 1980, 29 yrs. after onset
59. Chardot 103	female 48 1956	carcinoma uterine cervix	radium prior to infection; appendectomy done without touching neoplasm, due to diffuse infection	suppurating appendicitis with pelvic peritonitis secondary to radium application	vaginal cytology remained positive for 3 mos. after appendectomy thereafter negative; growth did not recur; N.E.D., in good health 7 yrs. later
60. Adekeye 3a; 583c; 583i	male 15 1976	extensive amelanoblastoma anterior mandible from left 2nd premolar to right 2nd premolar, marked displacement of incisors, cuspids & premolars	antibiotics (lincomycin for 7 days, no effect; then cephaloridine for 3 days) discharge ceased; mandible resected extra-orally	Staphylococcus aureus infection in tumor area; foul smelling pus discharging from gingival margins, pain; of 3 mos duration	healing was uneventful, deformity minimal; 7 mos. later surprising amount of hard bony tissue felt intraorally replacing resected mandible; 3rd molars had erupted; x-rays confirmed bone regeneration; N.E.D. March 1980, 7 yrs. after onset
61. Greentree 93; 297B	male 59 1957	large poorly differentiated squamous cell carcinoma bronchus, extensive spread into lung parenchyma, metastases to parabrachial lymph nodes, 20 lb. weight loss, (extensive necrosis of tumor present at surgery)	November 18, 1957 rt. pneumonectomy, mediastinal lymphadenectomy HN ₂ (24mg); oleothorax: 1200 cc sterile olive injected in rt. pleura	October 20, 1957 chill, fever, flu symptoms; 3 days later very severe pleural infection, with spiking fever (38.9° - 39.4° C); pus & oil drained (gram positive cocci and Staph. aureus); antibiotics given for 3 wks.	complete recovery but 1 yr. later psychotic depression required electroshock therapy; recovered, returned to work 1972; n.e.d. in good health until death of old age, 1975, 18 yrs after onset.

SERIES C, GROUP 2, INDETERMINATE (PROBABLE SUCCESSES): 27 CASES OF OPERABLE CANCER IN WHOM PYOGENIC INFECTIONS DEVELOPED SPONTANEOUSLY BEFORE OR AFTER SURGERY (16 CASES) OR WITHOUT SURGERY OTHER THAN BIOPSY (11 CASES): TRACED LESS THAN 5 YEARS
(Microscopic confirmation of diagnosis in most cases)

Doctor References	Sex, Age Date	Type, Site, Extent or Tumor	Type of Treatment	Type of Infection Duration, Extent	Final Result, Years Traced After Onset
1. Lambergen 421; 851, Case 66; 583K	female 34 1755	scirrhous carcinoma breast	infusions of belladonna for 17 mos.	suppuration in tumor, drainage from several fistulae	complete regression; patient remarried; had a baby, nursed it, traced well at least 3 yrs. after onset
2. Marteau 506, p. 15; 851, case 65; 583K	female 49 1760	scirrhous carcinoma breast, extensive infiltrating toward axilla	cathartics, laudanum, ass's milk, belladonna	erysipelas caused tumor to melt away leaving resistant nodule size of bean	end result unknown
3. Vautier 851, case 37; 583K; 892, p. 33	female 46 1812	mammary carcinoma size of turkey egg, nodular	carrot juice, hemlock pills; poultices of scraped carrot & hemlock leaves; "issue" opened on side of tumor	considerable decrease in size after "issue" was made, then very severe erysipelas developed on breast; suppurated 8 days, tumor softened, decreased markedly	complete regression in 1 yr.; patient became very robust; traced well 3 yrs.
4. Boyer 64, p. 21; 583K	female 46 1850	scirrhous carcinoma rt. breast, metastases in axillae; arm very edematous; cough, cachexia	mastectomy, both axillae dissected free of metastases	preoperative erysipelas around tumor; postoperative suppuration; rapid wound healing	gained weight; edema of arm vanished; no recurrence 8 mos. later; not traced thereafter
5. Collis 155; 583K	female 42 1855	scirrhous carcinoma lt. breast size of orange	mastectomy	erysipelas over all her chest, 6 days postoperative; left eye also inflamed	no recurrence 3 yrs.; later some cervical nodes enlarged; not traced
6. Mosengeil 306, p. 10; 560; 561; 583K	female 40 1869	mammary carcinoma of very rapid growth lymph node metastases	mastectomy; excision of some smaller metastatic lesions	erysipela in lower wound edge; 4 days postoperative, involved whole back & anterior thorax; rapid wound healing	no recurrence or further metastases 18 mos. later; not traced thereafter

7. Mosengeil & Hahn 306; 560; 561	female 40 1869	rodent ulcer or epithelioma lower eyelid, infiltrating neighboring tissues	finally excised as it was gradually extending	recurrent erysipelas infection each time caused cessation of growth & some decrease, then renewed growth occurred	not traced
8. Mosengeil 56; 125; 193; 307; 560; 561; 566; 894	sex? adult 1870	enormous epithelial canceroid of ear, very rapid growth	untreated (operation had been planned)	severe erysipelas on head	complete regression, not traced
9. Gillette 284	male 32 1880	recurrent sarcoma parotid region	primary excised from cheek; 2nd very extensive operation	severe facial erysipelas following 1st operation; prolonged suppuration of wound; rather intense suppuration after 2nd operation; 4 days later 2nd erysipelas; profuse discharge	no further recurrence; traced well & free from disease 3 yrs.
10. Heath 268	female 14 1883	fibrosarcoma involving abductor longus, gracilis, pectineus muscles thigh, size large pear; recurrence 2 mos. after operation; 2nd recurrence 3-4 years later in distal cicatrix	excision in 3 portions; pt. in shock after extensive operation; recurrence peeled off pubic ramus (incompletely)	fever for 10 days (100°-101°F.); wound suppurated (offensive pus); febrile 14 days after 2nd operation; wound again suppurated	patient in good health with local recurrence 5 yrs. after onset
11. Verneuill 246; 895	female 50 1885	epithelioma in region of trochanter (extensive, ulcerated)	operation by thermocautery, 2½ mos. after infection	erysipelas at edge of ulcerated growth, extended over thigh, abdominal region	tumor appeared worse, ulcer deepened; after thermocautery wound healed completely, no recurrence; not traced
12. Hutchinson 125; 344; 583K	female adult 1887	mammary scirrhus or adenoma (no biopsy)	untreated	very severe erysipelas (almost fatal)	complete regression; well, n.e.d. 5 yrs. later
13. Finney 123; 125, Case 32 in Table; 344, Case 18 in Table 3	sex? adult	epithelioma of nose, about 2.5 cm. in diameter	untreated	erysipelas	complete regression, no recurrence, traced well 2 years

SERIES C, GROUP 2, INDETERMINATE (PROBABLE SUCCESSES): 27 CASES OF OPERABLE CANCER IN WHOM PYOGENIC INFECTIONS DEVELOPED SPONTANEOUSLY BEFORE OR AFTER SURGERY (16 CASES) OR WITHOUT SURGERY OTHER THAN BIOPSY (11 CASES): TRACED LESS THAN 5 YEARS
(Microscopic confirmation of diagnosis in most cases)

Doctor References	Sex, Age Date	Type, Site, Extent or Tumor	Type of Treatment	Type of Infection Duration, Extent	Final Result, Years Traced After Onset
14. Beck 25	male adult 1893	extensive carcinoma lip and cheek	excision; plastic operation	2 attacks extensive erysipelas, postoperatively "wounds improved surprisingly"	1 yr. later old scar was healthy but tumors had recurred elsewhere; not traced
15. Weir 123; 127	male 23 1893	sarcoma of face attached to maxilla	surgical removal	erysipelas 2 days after operation	well, free from recurrence, 8 mos. after operation; not traced
16. Wyeth 946	female elderly 1894	ulcerated epihelioma of face, over right zygoma	untreated	facial erysipelas in ulcerated growth, arrested by scarifying skin just outside limits of growth	complete regression; local recurrence 8 wks later; not traced
17. Lomer 467; 583K	female adult 1896 or before	carcinoma breast	mastectomy	wound suppurated freely	free from disease 5 yrs. then axillary metastases; died pneumonia; autopsy showed cells of metastases very small, no mitoses
18. Brockner 137; p. 210; 138	female 71 1897	ulcerated epithelioma of face; 2 yrs. duration	untreated	severe erysipelas, fever 104°-105°F.	complete regression; healed in 2 mos.; traced 2½ yrs. later
19. Langhans 282, p. 636; 426; 583J	female adult 1900	recurrent chorionepithelioma vagina (primary had been curetted, base cauterized) onset after normal confinement	recurrence untreated	recurrent nodule became infected, green necrotic mass of tissue sloughed out	complete healing, no further recurrence; traced about 1 yr.
20. McMaster 486	male 48 1904	round cell sarcoma parotid	excision; more radical surgery soon after; considerable disability; 50 x-ray treatments	4 mos. postoperative developed small abscess	no recurrence; traced well 2 yrs.
21. Bolognino (Gennari) 56	female age? 1906	recurrent round cell sarcoma shoulder; primary extensively ulcerated when removed	curettage of recurrence	erysipelas 10 days after 2nd operation over entire breast, arm: necrotic tissue sloughed off tumor; healthy granulations appeared	well and free from further recurrence over 12 mos.; not traced

22. Williams 928, p. 38	sex? age? 116	epithelioma of lip	untreated	streptococcus	complete regression, end result unknown
23. Viliavine 899	male 57 1926	carcinoma penis, groin metastases	amputation, metastases biopsied; 2 large doses radium to groin	erysipelas 9 days postoperative, inguinal region, left leg, ulcer in rt. groin; 2nd erysipelas after radium, very high fever; didn't prevent recurrence, small metastases; 3rd attack erysipelas caused regression, healing	complete recovery; traced well 3 yrs.
24. Réding 520; 539; 693	male 63 1927	extensive carcinoma cheek	radium (no effect); excision	erysipelas in wound; fever 40°C for 4 wks.	traced well 1 yr.
25. Müllerder 258; 568	male 65 1930	carcinoma rectum, metastases to regional lymph nodes	radical surgical removal	very severe erysipelas; high fever for 2 wks.; recovery, gained 14 kg.	traced well 1 yr.
26. Nadeau 576; 589	male 81 1930	carcinoma of bladder, hematuria, tenesmus, clots (cystoscopy, no biopsy)	untreated	facial erysipelas over entire head, fever to 105.6°F., also parotiditis; fever to 105°F. for 10 days; on 13th day again acute parotiditis, febrile another 2 days	complete regression, gained weight; died of cerebral hemorrhage over 2½ yrs. later, n.e.d. at death
27. Fort 233; 255	male 55 1948	papillary carcinoma Grade II surrounding bladder neck, protruding into internal urethral orifice; larger growths on margin of vesical neck	fulguration of primary growths at intervals for 11 mos.; incomplete transurethral removal; recurrence; biopsy; bilateral uterosigmoidostomy	infection after final operation, spiking fever to 103°F., chills; abscess in l.l.q. incised, drained; septic temperature continued despite antibiotics; transfusions	died of infection 26 mos. after onset; autopsy showed no carcinoma anywhere

SERIES C, GROUP 3, FAILURES: 11 CASES. OPERABLE CANCER IN WHOM CONCURRENT PYOGENIC INFECTIONS DEVELOPED SPONTANEOUSLY BEFORE OR AFTER SURGERY (9 CASES) OR WITHOUT SURGERY (2 CASES)

Physician References	Sex, Age Date	Type, Site, Extent of Tumor	Type of Treatment	Type of Infection, Duration, Extent	Final Result, Period of Survival
1. Williams 583K; 931	female 45 1898	extensive scirrhus carcinoma breast; axillary involvement	untreated	erysipelas on affected breast; diseased tissue sloughed "clean away" leaving healthy granulations beneath; healed rapidly	no local recurrence; undestroyed portion of tumor in axilla spread rapidly; death, internal metastases
2. Siredey 258; 317, p. 282	male 50 1924	carcinoma rectum size of hen's egg	colostomy; large rectal mass removed; later anastomosis, closure of iliac anus; repair of sphincter	pelvic abscess, drainage	apparent cure; returned to active life 8 yrs., then thoracic, costal & pleuropulmonary metastases; disease generalized; death over 10 years after onset
3. Lindenstein 457; 583K	female 45 1930	carcinoma breast	radical mastectomy; radiation	extensive erysipelas 3 yrs. postoperative, not severe; 2nd attack 6 mos. later; 3rd attack Oct. 1931	developed pulmonary metastases, died 5 yrs later
4. Memorial Hospital 57; 123; 528	male 39 1931	osteogenic sarcoma femur developing in former giant cell tumor after heavy radiation, with pathologic fracture	curettage, x-ray therapy 1928 (over radiated); amputation	staphylococcus & pyocyanous infection in eroded tissues over tumor	recurrence in stump; metastases to groin; death 3½ yrs. after onset of osteogenic sarcoma
5. Morton 559; 583K; 589	female 55 1935	carcinoma breast	excision, radical mastectomy 2 wks. later; x-ray, 500r	wound infection, healed in 4 mos.	symptom free 16 yrs.; then metastases in axilla, rt. shoulder; death 20 yrs. after onset
6. Dunphy 215; 258	female 36 1936	adenocarcinoma sigmoid colon, extensive regional lymph node metastases; intestinal obstruction 3 mos. after onset abdominal cramps, melena	laparotomy, transverse colostomy; 1 mo. later, sigmoid lesion resected; colostomy closed 2 wks. later	large pelvic abscess following laparotomy, requiring colpotomy	well 15 mos.; readmitted 18 mos. after resection; large recurrence involving sigmoid; retroperitoneal tissues, lt. adnexa removed, permanent colostomy; asymptomatic 4½ yrs.; ventral hernia then repaired; N.E.D. except for small nodule along ureter (scar tissue?); died 1 yr. later peritonitis following laparotomy for recurrence causing obstruction, over 5½ yrs. after onset

7. Dunphy 215; 258	male 68 1940	adenocarcinoma lt. posterior wall of rectum, evidence of blood vessel invasion	abdomino-perineal resection, 3 mos. after onset	acute cystitis and abscess in posterior wound	8 mos. later perineal recurrence; further surgery deferred until 22 mos. after 1st, then radical perineal resection prostatectomy; thereafter, urinary incontinence; 2 yrs. later further perineal recurrence, further surgery refused; bedridden with ca when reported 1947, over 7 yrs. after onset
8. Memorial Hospital 528	male 11 1949	osteogenic sarcoma tibia	amputation	13 mos. after amputation localized furuncle on stump; opened, drained for 1 wk.	pulmonary metastases evidence 18 mos. after amputation; West Nile virus inoculation, HN ₁ , without benefit; death 3 yrs. after onset
9. Memorial Hospital 528	female 57 1949	osteogenic fibrosarcoma humerus, pathologic fracture, (11x7x6 cm.); diffuse swelling of arm	biopsy; x-ray; interscapulothoracic amputation	postoperative fever for several days; disoriented 2-3 days; small stitch abscess	death almost 3 yrs. after onset
10. Memorial Hospital 528	male 65	osteogenic sarcoma (medullary fibrosarcoma type) ilium	explored, biopsy hip joint; fusion; hemipelvectomy; x-ray to wound (3000r) no effect	mild post-operative pneumonia; aureomycin (profuse diarrhea); low grade wound infection; fever to 103°F. for 1 day; incision, drainage sinus tracts; low grade infection continued	pulmonary metastases; recurrent tumor fungated through hemipelvectomy wound; death 2½ yrs. after onset, 5½ mos. after hemipelvectomy
11. Memorial Hospital 528	female 51	metastatic malignant hepatoma (patient had had radical mastectomy for breast cancer, 1942); onset hepatoma 1952; also had uterine leiomyomas	primary hepatoma excised, also cholecystectomy; rt. lobe liver removed at 2nd operation for 2 metastases	excessive bronchial secretions aspirated through tracheostomy following 1st operation; draining sinuses discharged from wound for several mos. (mucopurulent) following hepatic lobectomy	normal life thereafter until 1963, then died of cancer involving lt. lobe liver; 11 yrs. after onset

SERIES C, GROUP 4, SUCCESSES—OPERABLE CANCER IN WHOM CONCURRENT INFECTION
DEVELOPED SPONTANEOUSLY AND COLEY TOXINS WERE ALSO ADMINISTERED: 8 CASES

Physician References	Sex, Age & Date	Type, Site & Extent of Tumor	Surgery or other Therapy	Type of Infection and Toxn, Duration	Final Results Years Traced After Onset
1. Memorial Hospital 123; 528	male 36 1906	round cell sarcoma tibia	biopsy, 10 x-ray treatments	45 doses toxins (Buxton VI) in 79 days; moderate reactions; infection in or near biopsy wound before and during toxin therapy	complete recovery; no recurrence or metastases; traced well 12 years
2. Huntington 80; 123; 144; 145; 150; 212; 583H	male 40 1909	osteogenic sarcoma clavicle	total excision of clavicle wound left open	slight wound infection healed in 3 mos. Coley toxins (Tracy XI) for 6 mos. i.m. in region of wound, reactions to 106°F.	no recurrence or metastases; in perfect health until 1926, then developed valvular heart disease, causing death 23 yrs. after onset
3. Memorial Hospital 123; 528; 583J	male 57 1920	thrice recurrent neurogenic sarcoma forearm	primary & 1st two recurrences excised; x-ray (20) for 3rd recurrence; explored; radium packs & tubes inserted; little effect; amputation	following x-ray 23 doses toxins (Tracy XI) in 34 days, 4 good reactions; amputation; postoperative wound infection, fever to 103.6°F.; suppuration; toxins resumed for 8 wks.	no further recurrences; in good health; died myocarditis, nephritis, influenza, 13 yrs. after onset
4. Mayo Clinic 57; 59; 523; 542B; 589	male 23 1920	reticulum cell sarcoma humerus	incisional biopsy; radium packs totalling 56,816 mch. to chest (cross fire) to supraclavicular & deltoid regions (severe radiation dermatitis); shoulder joint disarticulation; x-ray to infraclaviculoaxillary region and chest	coccygeal abscess 1915-20 drained pus; toxins (Parke Davis XIII) 4 doses; wound infected after radium inserted; foul discharge; toxins resumed briefly; further wound infection, discharge from sinus	n.e.d.; married 1930; cholecystectomy 1943; papillary tumor urinary bladder resected 1949; infected dermoid cysts buttocks, scrotum, extensively dissected 1950; slight arthritis; hypertensive, arteriosclerotic heart disease, coronary insufficiency; adenocarcinoma breast 1959, radical mastectomy; myocardial infarction, 3 episodes pneumonitis; basal cell carcinoma irradiated rt. shoulder excised 1960; coronary occlusion, myocardial infarction, May 1964; died Oct. 10, 1964, congestive heart failure, arteriosclerotic heart disease, 44 yrs. after onset.

5. Memorial Hospital 57; 528; 583H; 583K	female 11 1936	osteogenic sarcoma femur	radium packs (60,000 mch).; amputation	toxins (special Lilly) 10 i.m., 2 in tumor prior to amputation, no regression noted; post-operative stump infection (pyocyaneous) profuse discharge; 2nd course toxins, I.M.	no recurrence or metastases; obtained prosthesis; in excellent health over 27 years, then breast carcinoma, radical mastectomy, Jan. 1964; no evidence disease Jan. 1980, 44 yrs. after onset.
6. Memorial Hospital 57; 528; 583H	male 15 1939	osteogenic sarcoma femur (fibrocartilaginous type)	incisional biopsy; high thigh amputation	toxins (Parke Davis XIII) 2/25 to 2/29/39; dose increased rapidly to 12 minims; fever to 104°F; furunculosis stump next 15 years.	no recurrence or metastases; in excellent health 1980, over 41 years after onset.
7. Adelman (589)	male 74	squamous cell carcinoma bronchus with extension to adjacent lymph nodes causing obstruction of bronchus	pneumonectomy	concurrent extensive pneumonia, lung abscess, leukocytosis (16,000 wbc; 80% polymorphs); post-operative Coley toxins subcutaneously every 2 wks. later every 6 wks., 1962-1968	no recurrence or metastases; in excellent health 1968, In October 1970 lesion apparent in other lung; grew slowly; no further toxins; given cobalt therapy; and chemotherapy; rapid growth last 3 mos; died Oct. 17, 1971 from marked pulmonary insufficiency, over 9 yrs. after onset of lung cancer.

The following is the only determinate case of Hodgkins disease known to have developed a pyogenic infection:

8. Elting & W.B. Coley 123; 142, case 4, p. 655	male 23 1908	Hodgkins disease involving the cervical and axillary regions	2 excisions prior to toxins; x-ray for several months after toxins; 2 more operations; cervical, sub-maxillary & axillary dissections after toxins and radiation	toxins, Tracy X, after 3rd operation, marked temporary local and general improvement 10 days after final surgery severe streptococcal infection, pyemia, several abscesses in different parts of body	complete recovery no further evidence disease; later arteriosclerotic heart disease, death, heart failure 1938, 33 yrs. after onset
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SERIES C, GROUP 5, FAILURES—OPERABLE CANCER IN WHOM BACTERIAL INFECTION DEVELOPED SPONTANEOUSLY AND COLEY TOXINS WERE ALSO ADMINISTERED: 10 CASES

Physician References	Sex, Age & Date	Type, Site & Extent of Tumor	Surgery or Other Therapy	Type of Infection and Toxin, Duration, etc.	Final Result; Years Traced After Onset
1. Stewart 744; 123; 833; 583L	male 27 1909	recurrent round cell sarcoma psoas muscle, involving 8 cm. of ilium	surgical removal; x-ray for recurrence	erysipelas caused arrest of growth; toxins (Parke Davis XIII) subcutaneously, no reactions; toxins (Tracy XI) 1 marked reaction, total duration 4 weeks.	complete regression in 3 mos., gained 10 lbs.; well 7 mos., then rapid recurrence, death 1910, 2 yrs. after onset
2. Memorial Hospital 528; 583H	female 26 1927	osteogenic sarcoma femur; extensive pulmonary metastases present prior to toxin therapy	very heavy radiation: 102,000 mch. radium in 28 days, no effect; tumor explored; . curetted; 4 alpine lamp treatments; amputation	extensive pyogenic infection entire tumor area; pus sac 10 x 15 cm.; Dakins' solution; toxins (P.D. XIII) for 2 wks; begun 6 wks. after amputation	pulmonary metastases regressed markedly following toxins, but disease then rapidly progressed, death 6 mos. after onset
3. Memorial Hospital 57; 528; 583H	female 17 1931	osteogenic sarcoma distal left femur	x-ray (2100 r prior to toxins, 2100 r after toxins); amputation; revision of stump following osteomyelitis	12 toxin injections (P.D. XIII) in 19 days (9 i.m., 3 i.v.), moderate reactions; febrile prior to amputation; infection of stump; following fall, fracture greater trochanter osteomyelitis	lung metastases gave surprisingly few symptoms; death 1932, 1 yr. after onset
4. Memorial Hospital 57; 528; 583H	female 5 1932	osteogenic sarcoma tibia, atypical	exploratory osteostomy; amputation	low grade infection in wound and tumor; toxins (P.D. XIII) after amputation; (14 i.m. in 22 days)	recurrence on stump; death 10 mos. after onset, of widespread metastases
5. Memorial Hospital 57; 528; 583B	male 23 1935	Ewing's sarcoma femur	punch biopsy; radium packs (120,000 mch. in 2 wks.); amputation	30 toxin injections; 15 Coley (P.D. XIII), 15 typhoid; 8 produced good febrile reactions; some regression; complete arrest of pain; acute tonsillitis, fever 103°F. caused temporary relief pain due to spine metastasis	metastases to spine, skull; death 18 mos. after onset

6.	Memorial Hospital 528; 583B	male 15 1936	Ewing's sarcoma femur	3 biopsies; 2 aspiration, 1 incisional; (amputation refused); x-ray, (1500 r)	infection of bone in tumor area; considerable pus evacuated; pneumonia; fever to 103°F.; 21 doses Coley toxins in 1 mo. (P.D. XIII)	disease not controlled, death 16 mos. after onset
7.	Memorial Hospital 528; 583H	male 13 1937	fungating osteogenic sarcoma tibia	bone incised in Oklahoma, intractable hemorrhage; hasty biopsy—wound tightly packed amputation at Memorial Hospital	wound badly infected; fever 102°-102.4° F.; after amputation toxins (P.D. XIII) 10 i.m., 5 i.v., only 6 good reactions; further purulent infection stump	multiple pulmonary metastases; death 11 mos. after onset
8.	Memorial Hospital 528; 583H	male 15 1940	osteogenic sarcoma humerus	x-ray (4200 r in 3 wks.); shoulder joint disarticulation	upper respiratory infection; slight fever for 2 wks., post-operative fever to 105° F., atelectasis; sulfapyridine given; toxins (P.D. XIII) 12 in 16 days (5 im., 7 i.v.) good reactions from i.v.	pulmonary metastases, also to ischium; death 14 mos. after onset
9.	Memorial Hospital 528; 583H	male 14 1941	osteogenic sarcoma femur	aspiration biopsy; x-ray (6450 r.) 7 doses P32; mid-thigh amputation; 3 transfusions; revision of stump	toxins (P.D. XIII), 5 i.m.; no chills, slight fever, given after x-ray prior to amputation; postoperative wound infection, (pyocyanous), fever; radiation necrosis; hospitalized 5 mos.; 2 attacks erysipelas	pulmonary metastases; death 18 mos. after onset
10.	Memorial Hospital 528; 583H	female 37 1943	osteogenic sarcoma femur; 17 x 15 cm., pathologic fracture	3 aspiration biopsies; x-ray (1500 r); hip joint disarticulation; later palliative x-ray to stump; recurrence; chordotomy	prior to amputation, after x-ray: 5 large doses toxins (P.C. XIII, 4 in tumor, febrile reactions to 105°F.); postoperative low grade infection, abscess (Staph. aureus)	metastases to ilium; recurrence in stump; pulmonary metastases; death 17 mos. after onset
11.	Doniach et al. 210a; 589; 583J	female 31 1956	choriocarcinoma invading myometrium almost to serosa and right broad ligament including vein	curettage; severe intraperitoneal hemorrhage; resuscitated with transfusion (4 pts.); emergency laparotomy, bilateral salpingo-oophorectomy, transfusion (4 pts.); transfusion (12 pts.) for 2nd hemorrhage; x-ray to lungs (2500-3500 rads)	fever 100°-104°F., purulent vaginal discharge (E. coli) prior to laparotomy; injections of husband's leukocytes intradermally in arm, thigh; skin grafts from husband and other donor and own skin; well 2 mos. then vaginal hemorrhage from ulcerated metastases; 7 more injections husband's leukocytes in 8 mos. ending August 1957	pulmonary metastases evident May 1957, marked regression by October 1957, complete remission, NED until 1960, then cor pulmonale; sudden death from pulmonary embolism during cardiac catheterization; autopsy; mixed tumor and thrombus in pulmonary artery, NED elsewhere, death over 4 years after onset

SERIES D, OPERABLE CANCER PATIENTS IN WHOM PYOGENIC INFECTION WAS ACTUALLY INDUCED OR ENCOURAGED

Although only five histories were found of patients with operable cancer in whom a pyogenic infection was actually induced, it is probable that this procedure was used in a number of other cases, since several eminent surgeons advocated such treatment. For example, Da Costa stated: "Occasionally . . . suppuration cures a sarcoma. A study seems to indicate that more cases of sarcoma are cured after operation if the wound suppurates than if it remains aseptic, and it has been proposed to infect deliberately the wound with pus germs to lessen the danger of recurrence." (178) In the 6th edition of his *Modern Surgery* Da Costa stated: "After amputation Wyeth waits until the wound is nearly healed and then infects it by inserting a gauze drain saturated with cultures of *Streptococcus pyogenes*. . . It has been observed that an attack of erysipelas occasionally greatly benefits a sarcoma, causing large masses of the growth to soften or to slough and exposing a granulating surface. Busch noticed this in 1866, but the fact had been observed in the 17th century. Interest was decidedly awakened by Biedert's case of sarcoma of the pharynx cured by an attack of facial erysipelas. Da Costa then cited the work of Fehleisen, Lassar and Coley and in conclusion stated: "After removing a sarcoma in any region, the patient should be given courses of injections of Coley's fluid." (178)

As regards the beneficial effects of infections in preventing recurrence of operable cancer, the following comments are pertinent. In the discussion of a paper on fulguration Thiery stated that there was one point in the technic which those who practiced this method insisted upon which had impressed him. (855) This was the insistence that the wounds be left open or only loosely approximated with drainage. He noted that his former professor, Verneuil, had been severely criticized for not closing his wounds after mastectomies—"an unfair criticism—because he advised only that one amputate freely without worrying about whether it would be possible to close the wound." He performed extensive operations and often dressed his enormous wounds "à plat," when he could not approximate the edges by sutures. Suppuration then ensued, and Thiery stated: "I was often struck by the slowness with which recurrence developed in such cases . . . I observed recurrences 14 years after the primary operation in one case, at seven years in several and at four or five years in numerous other cases. . . I asked myself if suppuration, in eliminating the traces of cancer which had escaped the knife, did not play a role in delaying recurrence, and if therein lay the secret of success, which has been attributed in some cases to the radiotherapy and to fulguration." (855) These remarks were coldly received by the surgeons present at this meeting. Routier protested strenuously, calling this "a doctrine that would make surgery go backward." Tuffier joined in the protest and could not accept the doctrine of leaving wounds open, nor in the protective role attributed to suppuration. (855)

Vautier in his thesis on cancer (1813), proposed that in the early stages of malignancy one should open an "issue." As to this procedure, Tanchou, a distinguished Parisian

SERIES D, OPERABLE CANCER: INF. INDUCED: BRIEF ABST.

physician stated (1844): "One knows that often the affected lymph nodes and the primary growths disappear during the course of concurrent illness, never to return. . . It is according to this idea . . . that a large number of observers have advised establishing "issues" on diverse portions of the body and even in the wounds remaining after operation." (892) In this monograph on the treatment of mammary cancer, Tanchou stated: "One of several . . . issues were sometimes established on the arms, in the cancer or its periphery, before or after operation, with success." (851) He cited Mannes as stating that the application of four cauteries (issues) was consistently successful in his experience. Pouteau was also cited as having great confidence in this procedure. Dupré de Lisle reported many cases confirming this opinion. (217)

On April 1, 1901, Wyeth read a paper on amputation at the hip joint for sarcoma and its tendency to recurrence. He spoke of the extremely malignant character of sarcoma, pronouncing it the most malignant tumor. The effects of pyogenic infection and the induction of erysipelas were considered as they affected prognosis. From a study of his own and other cases, Wyeth concluded that streptococcic infection had an inhibitory effect on recurrence of sarcoma, and that it should be induced. He stated that infection should be induced at intervals of not more than six months for at least six years. In the light of present knowledge of toxin therapy this appears to be too long a period. A year may be sufficient. (949)

These observations of Wyeth are of historical interest. His belief that infection should be induced more than once, and not merely immediately after operation, indicates that he did not believe a single infection would produce a permanent result. The majority of cases treated by toxin therapy for four to six months remained free from recurrence. The optimum duration of treatment depends upon the type of tumor, the age of the patient and especially on the stage of the disease when toxin therapy is begun or infection is induced.

SERIES D, OPERABLE CANCER: INF. INDUCED: BRIEF ABST.

**SERIES D, OPERABLE CANCER, PYOGENIC INFECTIONS
INDUCED, BRIEF ABSTRACTS (5 CASES)**

The following five cases are given as examples of induced pyogenic infection in operable cancer patients. Brief abstracts are given first. The detailed histories are available at Cancer Research Institute.

1. (*Duparque*): Mme. B., female, aged 41, 1833; hard nodular tumor size small egg in breast, nipple retracted; prognosis very grave; operation refused; patient ordered to cease arduous work as laundress; venesection; leaches applied to affected breast, also emollient, resolvent compresses; hemlock and hydrochlorate of gold internally; *an "issue" was opened on left arm causing a suppurating wound; growth alternately increased and decreased for 6 months, disappeared by 8th month; end result unknown.* (216; 583k; 851)

2. (*Wyeth*): J.L., male adult, sarcoma superior maxilla involving floor of orbit, roof of antrum; onset 1893; tooth extracted; antrum explored; curettage (considered to be an abscess); no improvement; exploratory operation; condition found to be malignant: *attempts to inoculate erysipelas failed at first, then succeeded* (remote from tumor); *no improvement noted in growth*; radical excision upper jaw, including portion soft palate, floor orbital cavity; brief course Coley toxins; then injection in thigh of virulent culture streptococcus (Buxton's) caused erysipelas-like inflammation spreading over abdomen; *inoculations given for 2 months.* No recurrence; artificial jaw made with movable palate; patient resumed law practice; alive and well 1901. (946, p. 936; 949, p. 386)

8 yrs.

3. (*Wyeth*): Male, adult, 1895; extensive osteosarcoma proximal humerus; preliminary ligation subclavian artery to arrest hemorrhage from large growth; shoulder-joint amputation performed 3 or 4 days later; wound left open for subsequent pyogenic infection; *it healed slowly by granulation with extensive suppuration; 2 months later pure cultures Streptococcus erysipelatis injected following a brief course of Coley toxins,* as the toxin injections were believed to favor the development of infection; *two infections produced in this manner;* no recurrence for 5 years; then recurrence involving clavicle, scapula; Coley toxins resumed, *another inoculation of streptococcus given; very marked reactions; improvement in tumor and general condition;* patient up and about tending to his business 6 months later, over 6 years after onset; prognosis guarded; end-result not recorded. (583h; 946; 949, pp. 388-390)

6 yrs.

SERIES D, OPERABLE CANCER: INFECTION INDUCED

4. (Wyeth): Adult, osteosarcoma femur; hip-joint amputation; *wound allowed to become thoroughly infected with pyogenic organisms by leaving a large portion open and packing it with loose gauze*; no recurrence when last seen 3 years later. (Wyeth noted this was the only one of 5 hip-joint amputations for sarcoma which survived over one year, also the only one in which he had induced infection up to that time. (583h; 949)

3 yrs.

5. (Matagne): Female adult, 1902: cancer breast, (untreated); patient very impressionable, so no local inoculations given; *8 inoculations attenuated living cultures of streptococcus*, caused painful inflammatory indurations (furuncles); several had to be incised; further treatment refused; 3 months later breast removed surgically. No recurrence or metastases, 1905. (516)

3 yrs.

SERIES E, INOPERABLE CANCER PATIENTS IN WHOM AN ATTEMPT WAS MADE TO INDUCE A PYOGENIC INFECTION AND INFECTION WAS PRODUCED: 36 CASES

Type of Tumor:

10 carcinoma: #1, 4, 6, 7, 9, 10, 11, 18, 30, 36.

18 sarcoma of soft tissue: #2, 3, 5, 12, 13, 14, 16, 17, 19, 20, 21, 22, 23, 25, 27, 28, 29, 33, 34.

4 sarcoma of bone: #15, 21, 26, 32.

1 malignant melanoma: #35.

3 unclassified: #8, 24, 31.

Type of Infection:

34 erysipelas (by inoculation of living cultures in all but case 2 in which dressings which had covered the head of an erysipelas case were laid around the growth).

1 streptococcus other than erysipelas: #34.

2 suppuration: #1, 25.

1 complicated by abscess: #16.

1 peritonitis: #26.

1 septicemia: #27.

Effects noted:

12 complete regression: #1, 4, 13, 14, 16, 20, 21, 22, 25, 29, 33, 34.

20 marked regression: #2, 3, 5, 6, 7, 9, 11, 12, 15, 17, 18, 19, 23, 24, 27, 30, 31, 32, 36.

3 little effect: #10, 28, 35.

1 no apparent benefit: #8.

4 died of infection: #9, 10, 19, 27.

7 died of cancer: #8, 12, 14 (10 yrs.); 16 (10 yrs.); 22 (6 yrs.); 28, 35.

2 died of hemorrhage: #12, 15.

1 died emaciation following complete regression: #29.

17 not traced: #1, 2, 3, 4 (well 4 yrs.), 5, 6, 7, 11, 13 (well 2 yrs.), 17, 18, 23, 24, 30, 31, 32, 36.

5 traced well 5 or more years: # 20, 21, 25, 33, 34.

Other therapy given which may have stimulated or depressed the patient's natural resistance to the neoplasm.

Stimulated:

Systemic medication:

1 cod liver oil: # 12.

1 conium: #1.

SERIES E, INOPERABLE CANCER, BRIEF ABSTRACTS

3 Fowler's solution: #12 (caused several abscesses); 15 (caused 1 abscess); 23.

3 Coley Toxins: #16, 17, 32.

1 bacterial toxins other than Coley's: #34.

Surgery after infection: #17 (wound healing very rapid).

Surgery just prior to infection:

2 incomplete removal: #33, 34.

1 exploratory incision, growth stitched to abdominal wall: #29.

1 aspiration of ascites: #25.

1 incision exposing abdominal tumor, wound packed with non-sterile gauze: #25.

Decreased Resistance:

1 poor nursing and nutrition: #25.

3 repeated surgical procedures: #17 (8 operations); 32 (4 operations); 35 (6 operations).

Disease advanced or terminal before infection was induced:

2, 3, 5, 10, 12, 14, 15 (lung metastases), 19, 25, 28, 29, 35. (Note that only cases 14 and 25 regressed completely among this group and 25 was the only one that remained free from recurrence. He died of carcinoma of the liver 31 years after onset of the sarcoma).

SERIES E, INOPERABLE CANCER, PYOGENIC INFECTION INDUCED: BRIEF ABSTRACTS

This group comprises the known cases of inoperable cancer in whom attempts to inoculate erysipelas or other pyogenic infections were made and infection was produced, a total of 36 cases.

1. (*Schwenke*): Female adult, inoperable mammary carcinoma; patient had been treated by all the most effective remedies then in use, including conium, prepared by Storck's method, without effect; having lost all hope of cure she ceased treatment, shortly thereafter abscess formed on leg, suppurated; *as suppuration became more abundant, cancer diminished, then disappeared*; against advice patient allowed ulcer to heal; cancer at once recurred; *new "issue" then opened at site of former abscess on leg; when suppuration was well established, breast cancer again gradually disappeared*. End result unknown. (217; 583k; 851)

2. (*Busch*): Female, aged 19, 1866; enormous sarcoma cervical lymph nodes, very rapid growth, extending from insertion sternomastoid to cervical vertebrae, larynx and trachea pushed far to right (compression caused paresis of facial nerve); dressings from erysipelas patient laid around growth; patient transferred to contagious ward, put in bed notorious for frequency with which patients in it were attacked by erysipelas; skin over sternomastoid lightly cauterized; mild erysipelas infection developed a week later, fever to 40°C.; *tumor decreased markedly as soon as erysipelas developed; tense firm growth became much softer, more fluctuant; portions between sternomastoid and over parotid entirely disappeared in 2 weeks, facial nerve functioned normally; main mass of growth surrounding blood vessels reduced to small apple, freely movable*; patient developed toxemia during latter part of infection (due to absorption necrotic tumor tissue); growth again began to increase, in 14 days reached size child's head; Busch again attempted to induce erysipelas, without success; within a month growth attained its former size; end-result unknown. (72; 87, 88; 125; 244; 307; 344; 566)

3. (*Fehleisen*): Female, aged 58; multiple fibrosarcoma skin of left gluteal region, number of nodules forming sack-like tumor of considerable size and weight; 1882; fresh culture *Streptococcus erysipelatis* inoculated into tumor by scarification; 61 hours later rigor, next morning fever 40.5°C.; erysipelas spread over area 30 × 30 cm., lasting 11 days; constant high fever for 48 hours, danger of collapse; *during first few days of attack superficial nodules softened, then began to shrink, finally disappeared; main mass of tumor swelled, became distinctly heavier while erysipelas lasted, afterwards it partially degenerated*, but improvement was not sufficiently marked to encourage further inoculations; end-result unknown. Note: Fehleisen is generally regarded as the first to induce erysipelas by actual inoculation as a therapeutic procedure in a cancer patient. (125; 243; 244; 245; 344; 566)

SERIES E, INOPERABLE CANCER, BRIEF ABSTRACTS

4. (*Fehleisen*): Female, aged 49, thrice recurrent mammary carcinoma; 3 operations, last one December 29, 1880; recurrent growth 5×6 cm. in cicatrix, firmly adherent to reddened skin; several small nodules below and anterior to larger one; September 15, 1882, inoculations in 5 places; rigor 29 hours later, by which time erysipelas had spread over whole tumor: *severe infection over most of thorax, slight pleuritic effusion; by 5th day larger growth had decreased 50%, smaller ones no longer felt; by 9th day all tumors had entirely disappeared*; infection lasted 2 weeks, perfect result, no recurrence 2 years later, 4 years after onset. (244; 245; 583k)

5. (*Fehleisen*): Female, aged 8; recurrent inoperable intraocular sarcoma involving right masseter and submaxillary lymph nodes, right eye enucleated; recurrence in few weeks filled whole orbital cavity invading forehead at inner canthus; October 7, 1882, inoculation in region of tumor (skin lightly scratched in 6 places, culture rubbed in); rigor 24 hours later, fever $39.6^{\circ}\text{C}.$; *erysipelas spread over tumor, right forehead down to submaxillary region; main growth became intensely red but no smaller, lymph node metastases decreased 50%*; no further regression; two more inoculations attempted, but erysipelas not again produced. End-result unknown. (125; 245; 566)

6. (*Fehleisen*): Female, aged 51; advanced mammary carcinoma size of 2 fists, metastases axilla and skin near breast, around scapula; October 14, 1882; inoculations (6 small scarifications, all became infected); severe rigor 19 hours later; *erysipelas spread over whole breast to scapula, finally over right shoulder, upper arms; fairly large right pleural effusion, required aspiration twice; 8 nodules disappeared, 5 others remained although erysipelas had spread over them; by 4th day main growth had decreased markedly, by 15th day had decreased 50%*; no further regression. End-result unknown. (125; 245; 344; 583k)

7. (*Fehleisen*): Female, aged 40; twice recurrent mammary carcinoma, axillary and cervical metastases; 1st operation 6 years before, 2 others since; November 9 1882: inoculations; rigor 15 hours later; high fever for 11 days; *erysipelas spread over whole anterior surface thorax and shoulder to spine, down arm to hand; metastatic nodule softened, became fluctuant; opened, discharged 10 cc. necrotic tumor tissue; "yellowish-white-pus-like fluid"*; this nodule shrank after incision; no other effects noted. End-result unknown. (125; 245; 344)

8. (*Thiersch*): Age and sex not stated: "malignant disease"—site and type not given; 1883: patient inoculated twice (scarification), in both instances erysipelas produced, "no influence upon the disease." Patient died of cancer. (125)

9. (*Janicke & Neisser*): Female, aged 40; mammary carcinoma, very rapid growth; operation 10/82, recurrence 3 months later, spreading into soft tissues in pectoral, axillary regions; arm swollen, pain unbearable; May 20, 1883: inoculation in skin over tumor (scarification); rigor same day, *severe erysipelas spread over entire thorax, no suppuration; patient died on 4th day; tumor changed considerably in appearance, consist-*

SERIES E, INOPERABLE CANCER, BRIEF ABSTRACTS

ency; diminished in size, much softer, overlying skin wrinkled. Post mortem: tumor had almost completely disappeared, "tumor cells apparently destroyed by direct action of microbes; destruction was not yet complete;" cell nests had been invaded by columns of micrococci which had penetrated between the cells and surrounded them; in places carcinoma cells were paler and less distinct; when cut tumor appeared to consist of connective tissue trabeculae separated by collections of serum; there was no suppuration. (344; 355; 566, p. 39)

10. (*Feilchenfeld*): Female, age not given; far-advanced recurrent scirrhus carcinoma of breast widely involving chest, extensive metastases in axillary, cervical, clavicular lymph nodes; July 1887 inoculation: *severe erysipelas over entire trunk, down one arm; patient apparently died of infection*; post-mortem: "tremendous concentration of streptococci in carcinomatous tissue, as compared with normal tissues." (246; 583k)

11. (*Holst*): Female, aged 40; infiltrating ulcerated carcinoma of right breast, involving entire right chest, recurrent few months after mastectomy; August 1887; inoculations with attenuated cultures streptococci, later fresh cultures from Fehleisen used in and around tumor area; *latter caused erysipelas to spread over entire chest, back, with high fever; entire ulcerated area diminished; immediate effects striking though temporary*; end-result unknown. (125; 193; 260, 337; 344; 583k)

12. (*Kleeblatt*): C.F., male, aged 54; recurrent lymphosarcoma of tonsil and neck; growth size of child's head above scapular region; deglutition difficult; recurred after extensive operation; 45 injections Fowler's solution; 6 abscesses developed; incised, continued to suppurate for some time; did not seem to cause regression of tumors; patient almost moribund; severe erysipelas then developed spontaneously over neck, back, face; growths in tonsil completely disappeared, growth over scapula decreased from size of child's head to pigeon egg; metastases developed 2 months later, left axilla, left carotid; March 7, 1888: erysipelas inoculations (scarification on both sides); *well marked erysipelas developed involving trunk; metastatic growths almost entirely disappeared*; recurrence again developed within a month; another inoculation failed to produce another erysipelas infection; disease progressed causing death November 18, 1888. (123; 307; 344; 383)

13. (*Kleeblatt*): P.B., male, aged 52; inoperable lymphosarcoma of neck, extending from mastoid process to inferior maxilla; injections Fowler's solution, *little effect other than producing an abscess*; July 22, 1888: *inoculations Streptococcus erysipelatis furnished by Koch caused erysipelas infection over chest, back of neck, back, scalp, but not face; growth completely disappeared in 2 weeks*; no recurrence when last traced over 2 years after onset. (56; 125, Case 28 in Table; 193; 260; 307; 344; 383, Case 2; 566, p. 40; 718, p. 207)

The following case was the first attempt outside of Europe to induce erysipelas as a therapeutic procedure in an inoperable cancer patient. W.B. Coley at this time was

SERIES E, INOPERABLE CANCER, BRIEF ABSTRACTS

unaware of the other cases cited above but discovered them while preparing his second paper in 1893.

14. (*W.B. Coley*): Mr. Z., male, aged 40; recurrent myxosarcoma of neck and tonsil; at 3rd operation growth extensive, only partial removal possible; general condition poor, tonsillar tumor so large that deglutition solid food impossible, liquids only with difficulty; May 3, 1891; 16 inoculations gelatin and bouillon cultures *Streptococcus erysipelas* failed to induce an infection but some regression occurred, also improvement in general health; inoculations discontinued August and September 1891; growth immediately began to increase in size, general condition deteriorated; by October condition locally and generally was as poor as when inoculations were begun; fresh culture then arrived from Koch's laboratory in Berlin; *severe attack erysipelas developed within an hour after inoculation; complete disappearance of growth except for cicatricial tissue remaining from previous operations. Patient gained weight and strength rapidly*; no further recurrence, general condition excellent; well 8 years, then developed cervical tumor, died in Italy 10 years after onset. (Whether this was late recurrence or 2nd primary is unknown). (124; 125; 130; 131; 143; 344; 583i)

15. (*Rovsing*): Male, aged 24; many-times recurrent sarcoma of humerus arising in the aponeurosis extending deeply in ulnar triangle, with pulmonary metastases; many operations for primary and recurrent growths; March 15, 1892: shoulder joint disarticulation only possibility, refused by patient; inoculations 2 day old cultures streptococcus taken from a fresh case erysipelas; no effect; 3 days later 2nd inoculation, 5 day old bouillon culture produced *chill, fever, typical erysipelas; area infiltrated by tumor became enormously swollen; old cicatrix ruptured on 5th day, rapidly discharged necrotic tumor tissue*; few days later severe pain in right chest, dyspnea, dullness over whole right chest. Aspiration indicated large hematoma in pleura which was evacuated; patient comfortable and well for few days; *extensive growth in distal arm had entirely regressed by discharge of necrotic tumor tissue through deep opening*; sudden death following more severe pain in right chest March 1, 1892; autopsy showed right pleura full of blood and tumor debris from 4 tumor metastases which had never given slightest symptom; had become necrotic and ruptured into pleura following effects of erysipelas, resulting in fatal pulmonary hemorrhage. (583h; 744; 838)

16. (*W.B. Coley*): G.K., male, aged 45; inoperable sarcoma skin of back 10 by 15 cm. in diameter, metastases size of goose egg in groin; metastasis excised, recurred in a month, grew rapidly; April 21, 1892: fresh culture *Streptococcus erysipelatis* inoculated into tumors, repeated daily every 2 or 3 days for 3 weeks; no suppuration or necrosis; *during 4th week new culture used, 2nd inoculation of which produced typical erysipelas, spreading over back, groin (inoculations had been made in both areas); remarkable change noted in tumor on back immediately after erysipelas developed*; it lost its lustre, color, shrank visibly in 24 hours; several sinuses formed next day, discharged necrotic tumor tissue; most prominent portion of tumor on back ulcerated (4 cm.) but rapidly healed; *both tumors disappeared in 3 weeks*; also had deep abscess on chest connecting

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with pleural cavity; 10 oz. pus evacuated; (this developed after erysipelas infection at site of injury sustained during early part of inoculations;) about 4 weeks later recurrent nodule at site of former growth on back; further metastases in groin; *inoculations of virulent cultures failed to produce another erysipelas until November 14, 1892 after 5 months' trial; this caused immediate marked regression; 50% in 36 hours, growth in groin and back again disappeared (in a week); 2 weeks later further recurrence, not controlled by further inoculations which caused 3rd attack of erysipelas;* Coley toxins then given (Buxton IV) for 2 months, causing complete disappearance of lesions on back and groin in 4 weeks; well 3½ years, then abdominal ascites, no further therapy; death 6 months later, 10 years after onset, 4 years after erysipelas was induced. (125, p. 493; 126; 131, p. 158; 143)

17. (*W.B. Coley*): B.N., female, aged 36; 7-times recurrent round cell sarcoma breast; 7 operations; final recurrence took place before wound had healed consisting of 3 separate growths 4, 5 and 1 cm. in diameter; June 2, 1892: *1½ gr. of 5-week old culture erysipelas inoculated into each of larger tumors, causing erysipelas infection; tumors broke down on 2nd day, discharged necrotic tumor tissue; marked regression; 1 nodule almost disappeared;* tumors began to grow again, others appeared in vicinity; inoculations repeated, but 2nd erysipelas infection not produced until July 2, 1892; lasted 11 days; *recovery very rapid; general condition good; all nodules diminished, some disappeared; effect again only temporary;* thereafter tumors grew very rapidly, were exceedingly painful; by October 1892, 3 large tumors present, largest size of cocoanut; 2 removed surgically; *3rd attempt to induce erysipelas unsuccessful;* during January and February 1893 injections of erysipelas toxins (filtrates) given; general condition remained stationary. End-result not recorded. (123; 125, p. 495; 583k)

18. (*Starr*): Female adult; mammary carcinoma, axillary involvement, several metastatic nodules on arm; 1892: *severe erysipelas induced by direct inoculation from fresh case; infection spread over breast, down arm; nodules in axilla entirely disappeared; improvement temporary;* end-result unknown. (125, Case 34 in Table; 583k)

19. (*W.B. Coley*): Male, age 65; extensive sarcoma of neck; patient had had very radical operation shortly before, general condition greatly impaired due to disease and to operation; December 1892: *inoculations attenuated cultures streptococcus failed to induce erysipelas; fresh culture from virulent case caused severe attack; patient died on 5th day; in this brief period tumor had decreased 50% by absorption, no sloughing.* (125, p. 505)

20. (*Boomer*): (Age and sex not given), sarcoma of neck size of orange; 1892: *inoculations of cultures of Streptococcus erysipelatis, tumor entirely disappeared;* no recurrence; alive and well 8 years later. (137)

21. (*Truit*): Mr. H., male, age 68, spindle cell sarcoma of left superior maxilla; left side of face extremely swollen, terrible pain, general condition affected; 1896: *bouillon*

SERIES E, INOPERABLE CANCER, BRIEF ABSTRACTS

cultures streptococcus injected directly into tumor in large doses with most severe general and local reaction; tumor disappeared completely; no recurrence; died sunstroke, July 25, 1914, at age 87, 21 years after onset. (123; 589)

22. (*W.B. Coley*): G.F.S., male, age 47; recurrent inoperable round cell sarcoma of chest wall, axilla, metastases in neck; 3 operations, 3rd incomplete; 3 recurrent nodules present when toxins (erysipelas filtrates) administered; no effect noted from these, prepared from attenuated cultures, nor from the filtered Coley toxins (*Streptococcus erysipelatis* and *Serratia marcescens*, Type IV) given 3 weeks; tumors then removed as completely as possible; June 1, 1893: 7 inoculations erysipelas cultures, then 4 cc. erysipelas filtrates injected; erysipelas infection developed, lasting 10 days; all growth regressed completely, condition much improved; disease recurred again, operation; pulmonary metastases, death August 12, 1895, 6 years after onset. (126; 457)

23. (*W.B. Coley*): J.H.S., male adult; extensive sarcoma of left thigh, involving pelvis; sedatives needed for pain, sleeplessness; July 3, 1893: inoculations given daily for 2 weeks before erysipelas was produced, fever to 104° F.; considerable improvement. End-result unknown. (528)

24. (*Sell*): Male, age 53; inoperable recurrent cancer of orbit and nasopharynx; 1st operation January 1893; hard large rapidly growing recurrence filled orbit forcing bulbus forward and downward; involved os nasale; fluid from bullae of patient with erysipelas injected subcutaneously in different places in tumor; 9 days later felt pricking sensation, heat; June 27, 1893: 2nd inoculation from same donor (mixed with glycerine); tumor grew, visible in nasal cavity; further inoculations using blood from ear at site of erysipelas in another patient, again without result; tumor continued to grow in all directions, invading hard palate; October 11, 1893: inoculations of blood from erysipelas area in another case injected into 4 or 5 areas beneath skin of tumor; in 9 days fever, slight headaches, increased redness locally; improvement then occurred, severe pains subsided; tumor regressed markedly (to one third its former size,) appetite and general condition also improved; January 1894, another inoculation; no effect; appeared almost normal by April; improvement temporary; tumor again began to grow; another inoculation tried October 1894 without effect; tumor growth rapid, patient cachectic and bedridden when Sell reported the case; end-result unknown. (778)

25. (*Wyeth*): J.P., male, aged 35; intra-abdominal sarcoma; exploratory operation; August 23, 1893: wound deliberately packed with non-sterile gauze, causing extensive suppuration; growth regressed completely except for fibrous stroma; no recurrence; developed carcinoma of liver, 1923 causing death May 30, 1924, over 31 years after onset of the sarcoma. (589; 949)

26. (*W.B. Coley*): Male, age 48; enormous sarcoma of femur and pelvis; September 1893: erysipelas infection induced by inoculation; slight temporary decrease in size; death 2 months later; autopsy; abdomen filled with pus. (125)

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Note: After 1893 W.B. Coley (with one exception in 1901) ceased attempting to induce an actual erysipelas infection, but continued his research on the effects of the mixed toxins of *Streptococcus pyogenes* and *Bacillus prodigiosus* (now known as *Serratia marcescens*). Coley believed that these mixed toxins were safer and more predictable in their effects than inoculations of living cultures of streptococcus.

27. (*Selva*): O.M.M., male, aged 69; extensive mixed cell sarcoma of right thigh, considerable myxomatous tissue, of 4 years duration; had been operated once; prior to inoculation, skin over tumor shaved, corrosive poultice applied over night, then on October 5, 1893, streptococcus inoculated (5 or 6 scarifications); no result from 2 such inoculations a week apart; on 1/21/93 tumor again inoculated by scarification and injection using culture obtained from Coley; *a circumscribed erysipelas infection then developed* (30 × 33 cm.); *part of tumor sloughed away, general condition improved*; 4th inoculation a week later, same technic, using 5 cc., caused fever 103° F., 2 days later pedunculated portion of tumor size of orange sloughed off, leaving granulation tissue; 5th inoculation, 3 days later (2.5 cc.) injected subcutaneously, 1 cc. into tumor; right thigh increased in size; marked reaction, chills; tumor then softer, flabbier, more movable; stimulants failed to rally patient; October 6, 1893, death; autopsy: general streptococcal septicemia proceeding from tumor, with extensive slough; no evidence retrograde changes at a distance from the slough; but apparently increasing cellular activity. (779)

28. (*Selva*): E.D., female, age 35; extensive sarcoma of neck, mastoid to clavicle; September 27, 1893: inoculations (scarification and subcutaneous injection); *circumscribed erysipelas developed*; *growth regressed somewhat*; no increase in size for three weeks; then hemorrhage from vein eroded by tumor in neck; thereafter rapid growth; disease progressed causing death December 11, 1895. (779)

29. (*Beck*): Miss S., female, age 17, enormous inoperable retroperitoneal sarcoma, originating in fascia, filling entire pelvis; prognosis very critical; great edema of labia and legs; exploratory operation, growth incised; profuse hemorrhage (only controlled by packing); December 1893: "growth stitched to abdominal wall to make it possible to bring the erysipelas into direct contact with it"; *3 erysipelas infections were induced by inoculations*; *each time fatty degenerated tumor tissue discharged, edema greatly reduced*; subsequent inoculations (attenuated cultures) failed to induce further characteristic erysipelas; after March 1, 1894, two doses pure erysipelas toxins injected into arm; *growth completely disappeared*; patient later became more and more emaciated; died May 15, 1894, 2 months after tumor had disappeared. (25)

30. (*Petruschky*): Female, adult; recurrent mammary cancer; *15 inoculations made, using very virulent cultures of streptococcus obtained from purulent peritonitis*; *11 separate attacks erysipelas induced, each typical, lasting 3-5 days, with fever*; in some cases preliminary injections anti-streptococcus serum were made, but did not confer immunity; *marked flattening of neoplastic nodes noted, but complete regression did not occur*. End-result not recorded. (583k; 668; 669)

SERIES E, INOPERABLE CANCER, BRIEF ABSTRACTS

31. (*Petruschky*): Age and sex not stated; inoperable cancer (type and site not stated): *inoculations of cultures obtained from same source as above case (a purulent peritonitis) caused an erysipelas infection, with marked regression of neoplastic nodules; growths did not disappear completely; end-result not recorded.* (667)

32. (*Kelley*): W.D., male, age 38, four times recurrent small round cell sarcoma of superior maxilla; 4 operations, 1st consisting of entire excision superior maxilla except for orbital plate; prompt recurrence each time; temporary improvement followed injections of Coley toxins; later no effect; 1901: *attempt to induce erysipelas infection then made; slight attack occurred, much improvement in growth for a time; then began to increase rapidly, involving large portion of cheek, nose, with exophthalmos left eye; x-ray treatment 3-4 times weekly for several months; growth checked, then decreased 75%.* End result not recorded. (134)

33. (*Matagne*): D.A., male age 28; inoperable small round cell sarcoma of groin; x-ray examination, exploratory operation, incomplete removal, portion remained adherent to crural vessels and extended into peritoneum; general condition good; January 1907: *streptococcus of erysipelas inoculated, causing severe peritonitis, fever 40.5° C.; erysipelas spread over entire abdominal wall and both thighs, fever lasted 3 weeks (minimum 39° C.); complete regression intraperitoneal and crural involvement; no recurrence; alive and well, 1922, 15 years after onset.* (519)

34. (*Stewart*): D.V.W., female, age 26; leiomyosarcoma of uterus; exploratory laparotomy; vagina filled with tumor masses; cystic left ovary removed, hysterectomy impossible, pedunculated tumor mass attached to uterus partially removed via vagina by morcellement; extensive involvement surrounding urethrae extending into all fornices untouched; November 4, 1920: *hoping to induce streptococcal infection, vagina was packed with gauze from infected leg ulcers, left 6 days; on 4th day, fever (to 102° F.), remained elevated 6 days; apparently true erysipelas infection did not develop; during January and February 1921, injections of toxins (type unknown); caused febrile reactions of 100° to 105° F.; all bleeding and discharge ceased; infiltrating growth entirely disappeared; regained former health; well 13 years, then developed symptoms regarded as possibly a recurrence; x-ray (4800 r) concurrent with fever therapy (8 to 104° F.), further x-ray (2400 r) remained well though apprehensive about her health, working full time; 1954 developed arteriosclerotic and hypertensive heart disease; died bronchopneumonia and coronary occlusion, May 5, 1964, over 33 years after onset.* (528; 583i; 589)

35. (*B.L. Coley*): L.S. female, age 39; recurrent inoperable malignant melanoma with multiple metastases on the right posterior thorax, shoulder, both axillae, both cervical regions; enormous fungating growths, bled easily when dressed; patient had had 6 operations. January 27, 1948, *2nd inoculation of streptococcus caused severe erysipelas,*

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fever (to 106° F); condition critical; transfusions, penicillin, protein therapy; during and immediately following infection tumor areas felt more comfortable, well marked decrease, tumors appeared smaller, cleaner; regression only temporary. Disease not controlled by further inoculations, both streptococcus and Serratia marcescens cultures into tumor masses, although upper tumor again flattened somewhat; death May 4, 1948 over 3 months after first inoculation. (528)

36. (Firor): Elderly male, inoperable carcinoma of neck; 1955: *erysipelas successfully induced by inoculation; marked regression; improvement temporary; end result unknown.* (589)

Comment

In evaluating the effects produced by inducing infection in inoperable cancer patients, it is evident that better results were observed in the younger patients or in those whose neoplasms were not too extensive or before metastases had developed. That an infection so induced might prove fatal is evident for four of these 36 patients died of their infection.

SERIES F, THE EFFECTS OF INOCULATIONS OR SURFACE APPLICATION OF LIVING PYOGENIC BACTERIA, PRINCIPALLY ERYSIPELAS, WHEN INFECTION IS NOT PRODUCED: 31 CASES

Introduction

Before presenting the abstracts of these cases, it may be of interest to review the experiences of Petruschky (1897) and Besredka (1923).

Petruschky's studies indicated that both experimental and clinical streptococcus infections may vary greatly. He tried without success to induce an erysipelas infection in several cancer patients by repeated inoculations with cultures obtained from erysipelas patients. He then tried to increase the virulence by successive passage through mice and rabbits. These inoculations, even in large doses, were entirely unsuccessful.

Soon after this, he made inoculations with cultures obtained, not from an erysipelas, but from the pus of a purulent peritonitis in a female, aged 18. He thus produced a typical erysipelas. This occurred in two cancer patients, but under the same conditions five inoculations in a male patient with sarcoma failed to produce an infection.

Petruschky concluded that erysipelas in man may develop from a streptococcus other than erysipelas, and that streptococcus is not specific and may provoke mild or severe infections varying greatly from one another. His conclusions:

1. That erysipelas develops only when inoculation is made in the lymph spaces of the skin and mucous membranes.
2. The virulence of streptococcus for man is not at all comparable to its virulence for rabbits.
3. The resistance or immunity of patients is very variable and this may explain the variable results obtained. Thus in trying to produce experimental erysipelas in man one must proceed prudently, using mild cultures at first before trying virulent ones.
4. The existence of other diseases prior to inoculation greatly modifies the susceptibility of the patient as regards streptococcus infection. Thus diphtheria, scarlatina, tuberculosis, measles, typhoid fever, all seem to diminish the resistance of the patient to induced streptococcus infection, while cancer and sarcoma seem to increase it. (667, 668)

Besredka and Urbain reported on their experiences regarding the development of local immunity to streptococcus (38). They noted that this was in all points the same as reported earlier with staphylococcus.

These two organisms when grown in liquid media diffuse a specific substance *sui generis* which acts electively on the skin. Applied on the surface of the skin in the form of a wet dressing, it "vaccinates" guinea pigs against a cutaneous lesion, as well as preventing death from lethal doses inoculated subcutaneously.

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This immunity is established with a rapidity which excludes the concurrence of antibodies elaborated by the animal. (Is it due to interferon stimulation or release?)

The material was prepared as follows: The streptococcus culture was inoculated into a bouillon serum and kept at 37°C. for 8 to 10 days. This second culture, less luxuriant than the first was filtered through a bougie. In the filtrate thus obtained streptococci were no longer growing. This product was used for the skin applications and the injections.

The streptococcus used in preparing this filtrate in 18-24 hour cultures killed a guinea pig of 400 grams within 24 hours in doses of 2 cc given subcutaneously.

Besredka concluded from his experiments on guinea pigs that in old cultures of streptococcus there is formed a substance which is endowed with special properties. This substance has no effect when injected by the intraperitoneal route but exerts an appreciable action when injected subcutaneously. *However, its action is most manifest when one applies it on the skin as a wet dressing:* within 24 hours guinea pigs are thus "vaccinated" not only against a cutaneous streptococcus lesion but against larger than lethal doses of virulent streptococci given subcutaneously. (38)

These early studies were among the first to suggest the importance of the skin as an immunologic organ. It would seem worthwhile at present to try applying attenuated bacterial cultures to the surface of accessible cancers such as breast carcinoma, basal cell carcinoma, or malignant melanoma, as a prelude to systemic injections of bacterial toxins given intravenously.

Series F

31 inoperable cases of malignant tumors in which an attempt was made to induce an erysipelas infection by inoculations and infection was *not* produced. Note that the effects upon the tumors in this series are *much less marked* than in the cases where an acute infection actually occurred either spontaneously or by inoculation.

For the most part these were recurrent, very far advanced tumors; two or three operations had been performed (6 cases); metastases were present (4 cases) or the patients were old and/or feeble (4 cases). Although in many of these 31 cases no beneficial effect was observed, in case 3 local external applications of streptococcus cultures caused marked local effects, debridement possibly due to streptococcal enzymes. There was considerable regression in seven cases, and in case 11, in which toxin therapy (Coley toxins) was also administered, there was complete regression, and the patient remained free from recurrence until death from cerebral hemorrhage, 24 years after onset. Thus no patient recovered as a result of inoculations of streptococcus cultures alone that did not induce an infection.

As to possible palliative effects in such cases, Finney cited his experience (case 9) as indicated "a point of great value" regarding such inoculations, namely the influence of the treatment in cases which may not finally result in cure, i.e., *as a palliative to reduce pain and make the patient more comfortable in the terminal stage.* "After the first reaction from the erysipelas (inoculation) the pain almost entirely disappeared and did not reappear with severity while the patient lived. She had been almost constantly under

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the influence of morphia up to the time of the inoculation and after it she had only a little codeine to relieve her cough, which persisted after the pain had disappeared.”

Types of Tumors:

carcinoma: cases 4, 6, 7, 8, 9, 12, 29, 30, 31.

epithelioma: case 13

sarcoma of soft tissue: cases 2, 10, 11, 15, 16, 17, 18, 24.

sarcoma of bone: cases 3, 5, 32.

malignant melanoma: case 1.

unclassified: cases 14, 19, 20, 21, 22, 23, 26, 27, 28.

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1. (*Bruns*): Young female; malignant melanoma cheek and cervical lymph nodes; two operations, 2nd incomplete; arsenic tried without effect; 5 inoculations pure cultures streptococcus erysipelas from different laboratories failed to induce an infection; disease progressed, death a year later. (72; 257)

2. (*Biedert*): Young female adult, recurrent sarcoma cervical, submaxillary lymph nodes involving pharynx; several operations, repeated recurrences extending around neck to vertebrae; repeated attempts to induce erysipelas by scarifications, injections into neck and pharyngeal growth failed; bandages and sheets from erysipelas patients also applied unsuccessfully; disease progressed, causing death (72).

3. (*W.B. Coley*): M.B., female, aged 16; very extensive round cell sarcoma lower femur size child's head; general condition bad; exploratory osteotomy; when inoculations were begun biopsy incision gaped widely, sarcomatous mass size of two fists protruded; inoculations given for 5 to 6 weeks in doses up to 20 minims; *sloughing granulation tissue on tumor rapidly cleared leaving bright granulating surface, much healthier in appearance: "antagonistic effect well marked;"* general condition unchanged, too weak to continue treatment; although infection did not develop, febrile reactions to 104.5° F., rapid pulse, chill occurred after 2nd injection; end-result unknown. (124; 125)

4. (*W.B. Coley*): Male, aged 75; recurrent inoperable carcinoma involving entire left face, adherent to bony structure; had been given 150 pyoktanin injections without effect; inoculated 3 times, using same stock cultures erysipelas that failed to produce an infection in Mr. Z. (Coley's first inoculation case, see Case 14, Series E); no effect resulted other than febrile reaction (102.3°F.), nausea, vomiting, *slight softening of tumor*; end-result not recorded. (124; 126)

5. (*W.B. Coley*): Female, aged 26; twice recurrent periosteal round and spindle cell sarcoma dorsal vertebrae; 2 operations; 2 subcutaneous inoculations, 1 into tumor in 2 places (about 3 cc.); *tumor became much more moveable, perceptibly smaller*; 2 more inoculations next day, 2nd being a dose of 50 minims; tumor then seemed to be swelling; 3rd operation 2 days later; end-result not recorded. (124; 126)

6. (*W.B. Coley*): Female, aged 40; thrice recurrent carcinoma left breast 8 × 13 cm., markedly protuberant, ulcerated; profuse discharge; also metastatic growth size of egg adherent to skin of right breast; inoculations for 2 months; moderate general reactions lasting 24-48 hours; *partial degeneration of tumor, considerable regression; general condition excellent, patient up and about most of the time*; erysipelas infection not produced though same cultures had produced infection in another case; after inoculations were stopped tumors soon began to increase; end-result not recorded. (125, p. 497; 583k)

7. (*W.B. Coley*): Male, aged 55; carcinoma cervical lymph nodes size small egg; operated 3 months before, rapid recurrence; repeated inoculations for 3 weeks using

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pure cultures *Streptococcus erysipelatis*; febrile reactions 101° to 103.5°F. but no infection occurred; *tumor broke down, discharged considerable necrotic tissue, decreased almost a third*; end-result unknown. (125)

8. (*W.B. Coley*): Male, aged 75; large metastatic carcinoma inguinal lymph nodes primary in penis; amputation of penis year before; metastatic growth size orange right inguinal region, patient very feeble, chronic bronchitis, weak heart; repeated inoculations *Streptococcus erysipelatis* caused febrile reactions to 103.5°F. but no infection; *partial degeneration of tumor, temporary improvement followed*; inoculations stopped as only attenuated cultures were available and patient was so weak; end-result unknown. (125, p. 498)

9. (*Finney*): Female adult; recurrent carcinoma both breasts, multiple metastases; distressing severe cough; involvement pleura, intense pain; pure culture erysipelas inoculated several times; *after first reaction pain disappeared (had been under morphia constantly prior to inoculation)*; *Thereafter only a little codeine needed for cough; good palliative effect noted though erysipelas was not produced*; died 2-3 months later from inanition (internal metastases). (123; 125; 131; 583k)

10. (*W.B. Coley*): Female, aged 2; recurrent extensive sarcoma orbit; repeated inoculations for 4 weeks; *only effect, slight transparency of cheek noted*; tumor then grew rapidly, death 5 weeks later. (127)

11. (*W.B. Coley*): M.B., male, aged 55: thrice recurrent inoperable sarcoma thigh; first operation fall 1891; recurrence in 5 months; 2nd operation, July, 1892; second recurrence in two months; 3rd operation, January, 1893; third recurrence in 1 month of very rapid growth, consisting of several hard movable masses on anterior thigh, marble to walnut sized; from March 14, 1893 to May 13, 1893 *Coley toxins* given, Type IV (mixed filtrates) and Type III (*streptococcus* filtrates), causing local and general improvement; last 2 weeks of June patient given subcutaneous *inoculations and local applications of erysipelas cultures (smeared over tumors)*; *true erysipelas not induced; no rise in temperature; area healed rapidly, regression begun during toxin therapy continued until complete; no further recurrence*; developed arteriosclerosis 1907, died cerebral hemorrhage, 24 years after onset, March 21, 1917. (528; 589)

12. (*W.B. Coley*): Female, aged 55; recurrent carcinoma breast; cultures *Streptococcus erysipelatis* inoculated; *developed acute pleurisy, died on 6th day*. (127)

13. (*W.B. Coley*): N.D., male, aged 50; epithelioma entire left side face; involved superior maxilla, almost complete ankylosis, deglutition solid food impossible *repeated inoculations bouillon cultures of erysipelas caused decided regression*; erysipelas not produced although large doses of virulent cultures used, causing mild febrile reactions (100°F.); later *Coley toxins* (Type IV) for 9 weeks; during one week when injections were suspended, tumor grew markedly; condition too weak to continue treatment; disease progressed, date of death not given. (127)

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14. (*Park*): Female, age not given; inoperable cancer, site not stated; patient put in contagious ward; direct inoculations from two patients with facial erysipelas failed to induce infection; end-result unknown. (127, discussion)

15. (*W.B. Coley*): Female, aged 26; inoperable sarcoma neck, pharynx, orbit; very rapid growth; inoculations living cultures streptococcus erysipelatis failed to induce infection; *no effect on growth*; death 4 weeks later. (127)

16. (*DeWitt*): Miss A., female, aged 19; twice recurrent round cell sarcoma abdominal wall, 20 × 23 cm; *attenuated cultures erysipelas inoculated, no effect*; 2 weeks later *virulent cultures caused chill, fever 105° F., quite ill for 72 hours*; no true infection developed, but *within 2 weeks tumor decreased remarkably* (8 cm. in diameter); *remained stationary four weeks*, then rapidly increased in size; excised; Coley toxins given thereafter to prevent further recurrence; patient in excellent health 10 months after 1st inoculation, not traced subsequently. (198)

17. (*Matagne*): M.J.G., adult, sex not given; extensive inoperable recurrent sarcoma of neck; operation; rapid recurrence; inoculations streptococcus cultures failed to induce erysipelas; injections Coley toxins (probably Buxton VI formula); *bulging tumor flattened down*; 2 months later, against Matagne's advice, a young surgeon again operated—patient died as a result of operation. (519, Case 1)

18. (*Petruschky*): Male adult, sarcoma, site and type not stated; 5 inoculations virulent cultures failed to induce any erysipelas; end-result unknown. (669)

19, 20, 21, 22, 23. (*Petruschky*): 5 female cancer patients (site and type not given), repeated inoculations different cultures streptococcus, some of which had been passed through rabbits to increase virulence, failed to induce any infection in these cases; *no effects* noted apparently; end-results not given. (669)

24. (*W.B. Coley*): W.J.P., male, aged 22; twice recurrent small round cell sarcoma gracilis muscle; (Coley toxins had been given briefly); following third incomplete operation inoculations of fresh bouillon cultures from a violent erysipelas given for 3 weeks; moderate febrile reactions (to 103°F.); no infection produced. Coley toxins then resumed for 8 weeks; *remains of growth apparently regressed*; 2 weeks after injections stopped, another recurrence; radiation then given for a month; (toxins resumed with radiation); growth regressed markedly, then remained stationary 1 month; began slowly to increase in size; 4th operation; 4th local recurrence; evidence pulmonary metastases; end-result unknown, probably died. (123; 134)

26, 27. (*Helstead & Cheewitz*): 2 cases (age, sex not given); inoperable cancer (type not stated); attempts to induce erysipelas with fresh cultures grown from a recent case of

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accidental erysipelas, failed, *no effects whatever*. End-result not given, probably death. (838)

28, 29, 30. (*Strandgaard*): 3 cases (ages, sex not given); 1 abdominal cancer, 1 rectal cancer, 1 advanced cancer lower lip which had deteriorated under radiation. Fresh cultures prepared from case of accidental erysipelas; hardly any reaction, though "great quantities injected." *No trace of improvement*. End-results not recorded, presumably all died. (838)

31. (*Strahlmann*): B.F., male, aged 45; metastatic osteogenic sarcoma, chondromyxoid type, primary left femur, pulmonary metastases 8 months after hemipelvectomy; antireticular cytotoxic serum, glycogen administered prior to attempt to inoculate erysipelas; three times inoculations made, using both scratch and intradermal method, in frozen and unfrozen areas; *absolutely no effect*; cultures were 18 years old, apparently inert; disease progressed causing death, 2 years after onset. (589)

Note: All but the last six cases in Series F were treated between 1887 and 1901.

SERIES G, INOPERABLE CANCER PATIENTS IN WHOM GANGRENE DEVELOPED LOCALLY EITHER SPONTANEOUSLY OR BY INOCULATION

Vautier (1813) in a thesis on cancer discussed the question of whether cancer is cured by the sole forces of nature. He had found several cases in searching the writings of the most careful observers, in which cancer had been terminated happily by gangrene. Among these was Richerand, who reported in his *Nosographie Chirurgicale* the case of a woman of "strong constitution" (see Case 7). Vautier added that a more recent case had come to his attention in which an old woman had developed an acute concurrent "adynamic fever" which cured her completely. He also cited Pouteau's opinion that cancer may be cured by "résolutive" (alterant) treatment. To confirm this view, Pouteau had reported the case of a woman who was cured of cancer of the breast by the appearance of an ulcer on her leg. Shortly after the ulcer cicatrized the cancer recurred. They then established an issue (a cautery) at the site of the former ulcer on her leg and the cancer soon disappeared a second time. (This appears to be the case of Schwencke in 1774 Case 1, Series E.)

He then cited Dupuytren's case (see above, Series A, Group 2, Case 3), in whom a scirrhus cancer of the breast became necrotic during an infection and was removed with forceps. He also cited another advanced breast case in whom, while the patient was being treated with hemlock and other remedies, she developed a severe erysipelas with suppuration lasting seven or eight days, who was cured. (The hemlock was continued for some time after the recovery from the erysipelas.) Three times thereafter there were slight symptoms of recurrence (pain, etc.) and these were dissipated by the application of leeches.

Vautier proposed the following treatment in cancer:

(1) In the early stages, a vegetable diet, open an issue (cautery); keep the bowels open; give light bleedings from time to time if the patient is plethoric; give carrot juice as the only fluid, give extract of hemlock gradually increasing the dose to very high dosage, which is then gradually decreased and then again increased, according to the results. Apply compresses of the crushed fresh leaves of hemlock. In winter (when hemlock leaves are not available) substitute a cataplasm of scraped carrot, mixed with powdered hemlock, cover with the skin of a swan (to maintain heat).

(2) If the disease long remains stationary in spite of treatment, or progresses, an operation should be performed, and thereafter the medication should be continued for a long period. (He reiterated this.)

(3) If the disease had advanced, is adherent to the ribs, with lymph node metastases—an operation is contra-indicated. "Prudence and duty command us expressly not to touch it in any way. One must limit oneself to general methods, palliatives—opium internally and externally alternating with the extract of *Jusquiame* (henbane or deadly nightshade). (892)

Cruveilhier stated that cases of "scirrhus, cancer and carcinoma and the tissues surrounding them are occasionally the seat of an acute inflammation—spontaneous, or

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induced by incisions or irritating applications. There results a melting away or gangrene of the affected tissues, followed by complete sloughing and a radical cure. (171) He added:

"Richerand cited a case of this kind. I also observed a case in 1811 at the Hotel Dieu Hospital, following an incision at another hospital. Another woman died as a result of the gangrenous process, succumbing with symptoms of adynamia. The same year I observed a case of a woman who had tumors of unknown origin all along her thigh, all of which successively sloughed out as a result of gangrene. There was a complete cure.

"Garneri reported a case of cancer cured by gangrene. In recent times it has been proposed that gangrene should be induced in order to cure cancer. Leveille has even inoculated gangrene with success." (171; 911)

Tanchou (1844) in a monograph on the medical treatment of malignant tumors of the breast, based on over 300 case histories abstracted or cited from the literature, discusses the role of gangrene as follows:

"It is remarkable that after hemlock it is gangrene that caused the largest number of cures. Gangrene may be considered as a therapeutic agent, whether it occurs spontaneously or is induced medically . . . Rigal of Gaillac induced gangrene in cases of scirrhus cancer by inoculating gangrene in a small incision or by applying gauze dressings soaked in gangrenous discharges on open cancers. One knows that Dussosoy had the idea of inoculating hospital gangrene in cancer patients after having cured an ulcerated carcinoma in a male aged 50. . . . The success of this audacious experiment was complete, the ulceration destroyed the entire tumor which sloughed off on the 19th day. Dussosoy added that he then concentrated on controlling the progress of the gangrene, succeeded in doing so and in a few days the ulcer became bright red and covered with healthy granulations." Tanchou added: "Here gangrene seems to have replaced live cautery, caustics or the scalpel." (851, p. 192-193; also Cases 49-54, pp. 76-88).

As to the influence of other types of concurrent infections (spontaneous or induced) Tanchou stated: "One knows that often the affected lymph nodes and the neoplasms disappear during the course of a concurrent illness never to return. . . . It is according to this idea . . . that a large number of observers have advised establishing "issues" on diverse portions of the body and even in the wounds remaining after operation." He cited the following case reported by Lévêque-Lasource as supporting this view:

"A male, aged 52, was operated upon at the Charité Hospital by Boyer for a scirrhus cancer occupying a large portion of the back. The growth recurred and the celebrated surgeon did not dare attempt another operation. Symptoms of inflammation developed, an abscess formed in the ulcerated growth, which suppurated freely, and the cancer was cured." (851, p. 207)

Elsewhere he stated that "one or several issues" were sometimes established on the arms, in the cancer ulcer or its periphery, before or after operation with success. Mannes stated that the application of four cauteries (issues) was consistently successful in his experience. Pouteau also had great confidence in this method of curing cancer. Dupré de Lisle reported many cases to confirm this opinion." (851, pp. 222-223)

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Fleschut in his thesis on cancer discussed the inoculation of hospital gangrene as follows: (253)

"A quite rare termination, and one which some practitioners regard as often favorable, is the appearance of gangrene in a cancerous tumor. We have indeed observed a small number of cases in which gangrene has caused the complete elimination of these tumors and produced an unhopd for cure. No further incentive was needed for the proposal to be made that gangrene be inoculated, in order to produce similar effects. Thus, in admitting the contagious properties of all type of gangrene, the destructive effects of this mortification should cease exactly at the limits of the tumor. Dussossoy seems to have been the first to try such an experiment (prior to 1787)."

Walshe (1844) in his treatise on cancer, stated: "In some rare instances spontaneous gangrene of the surrounding parts has led to the separation and expulsion of cancerous growths and been followed by complete recovery." (911) Walshe cites Garneri (181), Dupuytren (1829), and Richerand (1815), as well as Cline, Everard Home (1830), Steidale and others who have "observed this fortunate accident . . . Dupuytren considered it most likely to occur in cases of encysted cancer. . . . The separation of cancer in this way is not, however, certainly followed by recovery: Cruveilhier alludes to a case in which healthy cicatrization set in after the growth sloughed out, yet indurated masses soon made their appearance in the cicatrix, and though these were destroyed with chloride of zinc, the disease spread to the axilla." (911)

Walshe noted that the cicatrization of true cancerous ulcers has occasionally proceeded to completion, and a permanent cure resulted. Nicod (1810) reported such a case, and Bayle stated he had observed several.

"The inoculation of the matter of common and hospital gangrene has been practiced, with the design of imitating the natural processes of cure before referred to." (911)

Cruveilhier (1864) stated that inflammation was the cause of the most profound alterations in sarcoma. Such inflammation results almost immediately in gangrene (necrosis): in cases of superficial sarcoma such gangrene may be followed by a temporary cure if all the neoplastic tissue is thus destroyed. Inflammation of cancer tissue may result in suppuration associated almost always with partial necrosis or of complete gangrene "en masse."

He stated that he had "seen many patients with sarcoma who were temporarily cured as a result of gangrene, either spontaneous or induced, so that healthy cicatrization was produced in the manner of cicatrices of wounds that suppurate." (171)

He referred to the Thesis of Alphonse Robert, surgeon at the Hotel-Dieu Hospital, on *Altérations dont les tumeurs cancéreuses sont susceptibles*. (710) Cruveilhier first discussed the beneficial effects of gangrene in cases of cancer in 1816, having observed three such cases. (709)

Broca (1866) in his *Traité des Tumeurs*, discussed the effects of concurrent suppuration, acute inflammation and gangrene on cancer. (70) He began by stating that theoretically it was possible to believe that all vascular tumors could become inflamed. It would seem that tumors should be very often the subject of inflammation, since many of them are vascular and have weakness of the stroma, especially those external growths which are subjected to abrasions, pressures and in general, all mechanical irritations.

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Actually, however, cases of cancer proven clinically and pathologically to have concurrent acute inflammation are much more rare than one would expect.

He stated that acute phlegmonous inflammation, suppurative or gangrenous, was sometimes caused by trauma, sometimes occurred spontaneously. Acute inflammation of tumors may terminate by resolution, suppuration or gangrene.

The absorption begins by cessation of pain, diminution of the tumefaction, the tension and of the heat; sometimes this absorption is complete; that is, the tumor returns to its size prior to the inflammatory episode; occasionally the tissue of the tumor is so modified during the period of inflammation that the absorption of the tumor tissue as well as of the products of inflammation occurs. This favorable outcome which sometimes may result in a complete cure, sometimes in an amelioration that is more or less marked, is rarely observed except in special types of tumors. One knows that several therapeutic methods exert their actions on erectile tumors by invoking an inflammatory reaction which modifies their tissue, and which makes them more apt to be absorbed. Cysts may be, to a certain point, compared with erectile tumors, because inflammation, either spontaneous or induced, produces not only the obliteration of the cavity, but sometimes the thick capsule which surrounds the liquid thins out and is absorbed little by little. The method of macerating or crushing which has had some success in the treatment of hypertrophy of ganglia and certain other tumors, also works by the inflammatory reaction which is invoked, and which ultimately is followed by absorption.

The termination by suppuration, may occur in the most diverse tumors. The suppuration of cancerous tumors is quite rare.

Broca then discussed the effects of concurrent gangrene on cancer and epithelioma. He noted that it was much more common a phenomenon than one would gather from reading the published observations. Total gangrene is rare, but partial gangrene is quite frequent, and in the last two years, he had seen five or six examples at Bicêtre (a hospital in Paris) where the number of cancer patients was much less than was generally believed.

He questioned some of the published observations as being possibly mistaken diagnoses. He noted that gangrene can occur in the most diverse types of neoplasms; lipoma, erectile tumors, chondromas, fibromas. He cited cases reported by Hébert, Prat, Page (3 cases) and Larrey.

He then cited three personal observations of epithelioma in which concurrent gangrene occurred, of which he described one, (very extensive ulcerated, of 25 years' duration—see case history abstracted below, Series G, case 5).

In conclusion Broca stated that it was evident that most types of tumors could become gangrenous, and that this complication was not limited to carcinoma. Gangrene of tumors can be partial or total. In the latter case the elimination of the necrotic tissue leaves a wound which may cicatrize. But these cures which are attributed to an intelligent effort of Nature are very rare and they are no more and no less permanent than those obtained by operation, and he believed that they are obtained at the price of a greater danger.

Partial gangrene is much more frequent than total gangrene, and occurs most often

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in tumors that are already ulcerated. The gangrene may involve all the ulcerated surface, but when the eschar sloughs off, one realizes that the necrosis did not extend to the limits of the tumor. In other cases only a portion of the ulcerated tumor is affected and the course of the disease in these cases is scarcely modified.

Non-ulcerated tumors very rarely become gangrenous, and then only in very voluminous neoplasms.

Partial gangrene is often progressive so that it ultimately may destroy a whole tumor, bit by bit; from partial it becomes general. This occurred in a case of Abernethy's which Broca cited (see below, Series G, Case 5). He also mentioned the case of Bérard, which was just as well known, but which was reported so incompletely that it was difficult to consider it as conclusive. Bérard stated: "It happens, occasionally, that a cicatrix may develop upon the sarcoma tissue itself." He then describes the case of a woman in which the principal viscera were involved in round cell sarcoma which became cicatrized (no detail at all).

Broca noted that he had occasionally observed, during the terminal cachectic stage of the disease, that an ulcerated discharging carcinoma may dry up completely; nodules become pale, flatten down and dry up and appear to heal (70, p. 239).

He noted that there are two opposing forces in tumors: one of regression or destruction, and one of renewed growth. If the latter force is greater, the tumor increases in size in spite of ulceration, and this is what occurs most frequently. If both forces are in equilibrium, the tumor remains stationary, but if the destructive action is strongest, the growth diminishes progressively in size. It is very rare that this regression occurs throughout the entire ulcerated tumor, but quite often involves one portion of an ulcerated tumor, especially along one of its edges. The entire thickness of the tumor may be destroyed and then the underlying base, resting on healthy tissue, will cicatrize at that point. He then cited a case of a woman of 69 (who had died at the Salpêtrière Hospital), with a cancer of the breast which had been extensively ulcerated for a long time. At autopsy it was seen that the large ulceration, resting on an indurated base, was free from neoplastic cells (as seen at microscopic examination), except towards the center where there was one small nodule the size of a hazel nut, which had the structure of encephaloid neoplasms (round cells). The ulceration had destroyed all the cancerous tumor, except for this very small portion, which Broca believed would, no doubt, have also been destroyed. The ulcer had begun to heal along its borders, and might have healed completely, at least for a time, if the patient had lived a few weeks longer.

Broca noted that gangrene of tumors may present two forms: "dry" or "wet."

In discussing dry gangrene he stated that he knew of only two cases: one reported by Dupuytren and one personally observed. Both were scirrhus carcinomas of the breast. He concluded that dry gangrene was most apt to occur in tumors that are least vascular, markedly fibrous and very hard.

"Wet" gangrene occurs much more frequently and may manifest itself in many different types of tumors, especially those which are ulcerated. It sets in almost always at the surface of the ulcer, but it may develop in non-ulcerated tumors. In the latter case it is usually preceded by an acute inflammation which often extends to the entire neoplasm and tends to cause complete necrosis.

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Thus gangrene of non-ulcerated tumors is most often total rather than partial. Those of ulcerated tumors are frequently partial, but may become progressive and little by little destroy the entire thickness of the neoplasm.

Broca believed that gangrene of tumors was ordinarily spontaneous; that is, it did not depend on any appreciable extrinsic cause. The agents capable of producing inflammation may, in certain cases, produce gangrene. He cited the case of Dr. Lloyd, in which gangrene occurred after a simple incision was made into an extensive chondroma, and a personal case in which gangrene developed following an application of chloride of zinc, which had been used to cauterize a large fungating bleeding nodule which surmounted the upper part of ulcerated extensive epithelioma.

He then described in detail the case of Feu Rigal de Gaillac. Because the patient had refused operation, Rigal succeeded in inducing gangrene by making a small incision in the center of a very extensive mammary tumor. He then placed gauze dressings over the incision which had been soaked in gangrenous discharges. Three days later gangrene developed, progressed and completely destroyed the entire tumor (24 cm. in circumference). There was no recurrence when last traced 18 years later (see complete history below, case 6). It is of interest to note that Broca could not believe that this patient actually had a carcinoma. He believed it was probably an adenoma. However, the original report by Robert suggests that the condition was malignant.

Broca's observations, made before the discoveries of Pasteur and Lister, are of interest. He stated that gangrene was not a virulent affection, nor was it contagious or inoculable. He regarded the sanious discharges from gangrene as merely an irritant and stated that one would be seriously mistaken in assuming that by the application of such discharges, one could produce necrosis and gangrene of either normal or pathologic tissue at will. He concluded that the extrinsic agents capable of inducing inflammation could occasionally produce gangrene.

He then cited the case reported by Boyer of a Russian princess with breast cancer who was taken to the waters at Barèges, by a French surgeon, and who was "delivered of her tumor by a total gangrene" (her surgeon attributed this to the action of the waters). The wound healed completely, but recurrence developed with multiple metastases and death occurred a few months later.

Broca cautioned physicians against attributing any value to the various treatments which had been tried, such as cataplasms, lotions of soot water (Garneri), drugs including laudanum (Steidele), calcium chloride (Fristo, 1831), and suggested that they recognize that gangrene of tumors is a terminal phenomenon, purely accidental, that one can neither prevent nor induce at will.

He believed that "dry gangrene" occurred because of obliteration of the arteries, but he admitted this would be hard to prove.

The most frequent cause of "wet gangrene" was acute inflammation. This was especially apt to occur in the cases in which complete necrosis of tumors by gangrene occurred. Irritating extrinsic agents acted in certain cases as the exciting factor by producing an inflammation which terminated by gangrene. Ulcerated tumors are more apt to become inflamed than those which are non-ulcerated, and they are also more apt to become gangrenous. Gangrene develops most often in soft very vascular tumors,

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which present conditions favorable for the development of inflammation. All these points indicate that in many cases inflammation is the immediate cause of necrosis of tumors. Broca stated that in general, gangrene of tumors is an unfavorable complication. A few patients may benefit, but others become worse than they were and many succumb to the putrid infection, or to the weakening effects of too abundant suppuration. Partial gangrene is almost always "injurious" because, after the sloughing of the eschars the patient is not rid of his tumor and finds himself in the same condition as if he had had a partial excision. The wound does not heal, and the disease progresses. Total gangrene can be followed by complete healing, and if the tumor is the type that is not apt to recur, the cure may be definitive, as if it had been obtained by operation. But for tumors that tend to recur, the chances of recurrence are greater after gangrene than after operation, because surgical excision extends through normal tissues while gangrene, even when total, may leave untouched small fragments of neoplastic cells which give rise to recurrence. In Broca's personal experience he observed nine cases of partial gangrene in patients with carcinoma of epithelioma, while he never had seen a single example of total gangrene, nor had he heard of any in the preceding ten years in the Paris Hospitals (1856-1866).

Serious accidents may follow the development of gangrene. He cited Quesnay's fatal case and a personal one.

His final conclusion: "It would be superfluous to multiply examples to indicate that gangrene of tumors, attributed by those who love strange things to an intelligent effort of nature, is really a grave complication, often fatal, rarely curative." (70)

Possibly the "gangrene" described by these 18th and 19th century physicians was due to the "tumor necrosis factor" being activated by the many organisms present in these ulcerated extensive neoplasms in the pre-antiseptic days. (93b)

SERIES G, INOPERABLE CANCER PATIENTS IN WHOM GANGRENE DEVELOPED SPONTANEOUSLY OR BY INOCULATION: 22 CASES

1. (*LeDran*): Female, aged about 15; very extensive inoperable cancer left breast, of eight years' duration, very hard, moderately painful, very dark red, beginning ulceration; *gangrene then developed*: in 2 days entire tumor detached itself and sloughed off in one mass during night, with profuse hemorrhage, leaving black almost circular wound 20 cm. in diameter, *suppuration followed*; for 5 weeks wound healed normally; then recurrence in center of unhealed portion; disease progressed, causing death 7 or 8 months later. (70; 435; 583k)

2. (*Quesnay*): Female, adult; enormous mammary carcinoma; overlying veins engorged; tumor ulcerated, *putrid suppuration*, soon *gangrene involved entire tumor*; "This mortification could have been advantageous to the patient, for it could, as we have seen sometimes, destroy the whole tumor, procuring a salutary amputation without pain, if the engorgement had not been so considerable; but the infection which this putrid gangrene carried probably caused septicemia . . . and other accidents which caused her death." *During the infection the tumor became quite soft and almost painless.* (583k; 690; 943, Vol. III, p. 484)

3. (*Amoureux*): Female peasant, aged 36; extensive ulcerated mammary carcinoma, overlying blood vessels varicose; nipple retracted; lancinating pain; *septic cataplasm applied to breast in order to produce suppuration*; vast deep ulcer developed, indurated, everted borders sternum to axilla; hemorrhages occurred due to necrosis of vessels in breast; belladonna and other herb lotions applied; venesection on foot; *laudable suppuration established*; *cicatrization then began*; "complete cure in one month." Not traced. (11; 851, Case 67) *Comment*: This is the first known case in which any form of infection was induced as a therapeutic measure in a case of cancer. Busch, in 1868, over 100 years later, was the first to induce erysipelas in such a case. It is of great interest to note that the macroscopic changes produced in the neoplasm during the gangrene infection in Robert and Rigal's case (see below, case 6), "fatty degeneration" and a "yellowish fluid" are very similar to those noted by other investigators such as Janicke and Neelsen, Coley and Moullin, 80 to 150 years later, following erysipelas infection or Coley toxin therapy. It is also of interest that in 1844, many years before Pasteur's work on micro-organisms, Tanchou stated in citing Robert's quite famous case: "This splendid observation leaves nevertheless some doubt in one's mind: can gangrene really be 'inoculated'? Perhaps this method needs to be given further trial." (583k; 851)

4. (*Dussossoy*): Male, aged 50; ulcerated carcinoma (site not stated); "hospital gangrene" inoculated; *ulceration destroyed entire tumor which sloughed off on 19th day*; in few days ulcer became bright red, covered with healthy granulations; *success complete—apparent cure.* (253; 583k; 851, pp. 192-193; 943, Vol. III, p. 484)

SERIES G, INOPERABLE CANCER, GANGRENE

5. (*Broca*): Male, adult; extensive ulcerated inoperable epithelioma face, involving entire left half, of 25 years' duration (extremely slow-growing); had destroyed left side of mouth, most of nose, all of left cheek and underlying bone; left eye invaded; "gangrenous inflammation developed; mass which filled orbit sloughed out, leaving large opening exposing large area of brain; death occurred next day. (70, Vol. I, p. 254)

6. (*Robert and Rigal*): Mme. B., female, aged 37; extensive far-advanced cancer breast, over 60 cm. in circumference at base; uneven, nodular, immovable, varicose overlying veins; lancinating pain; cachexia; operation refused; *gangrene inoculated*; small incision in center of breast, covered with dressings soaked in gangrenous discharges; in 3-4 days wound inflamed, odor putrid; *gangrene developed in center of tumor, progressed so rapidly that in 18 days the appalling tumor mass was entirely destroyed*; 2 of the affected lymph nodes the size of fists showed fatty degeneration, *carnified in certain spots, containing in their ulcerated centers a yellowish fluid*; dry dressings applied to wound left after tumor had been destroyed by gangrene; this took 4½ months to heal; *in order to prevent recurrence 2 setons were established before the cure was complete; traced well and free from recurrence 18 years later.* (583k; 711, p. 155; 851, Case 49)

7. (*Garneri*): M.M.M., female, aged 59; inoperable ulcerated nodular scirrhus carcinoma of breast, far-advanced, extensive, infiltrating axilla; lancinating pains, of 7 years' duration; overlying skin red, later purple; tumor involved entire left breast, ulceration in center 6.5 cm. wide, indurated, elevated, everted edges; base hard (true scirrhus); marked cachexia; local applications soot, lime water, etc. caused *inflammation, then gangrene of ulcerated area; became "putrid"; entire tumor mass necrotic, surrounding tissues unaltered; necrotic tumor tissue sloughed, gradually base of tumor changed into simple wound, cicatrization complete in about 3-4 months; regained perfect health*; no recurrence; died 4 years later, from an "adynamic fever." This observation led Garneri "to search for a substance capable by its application of gently destroying the life of cancer tissue." He added that "when such necrosis has been induced in ulcerated cancer, one should not attempt to limit it, but on the contrary, to encourage it until it has destroyed the entire neoplasm." (278; 583k; 851, Case 50)

8. (*Amard*): Female, aged 45; ulcerated cancer breast; *gangrene, necrosis developed; eschar formed which sloughed heavily, leaving healthy ulcer, no longer characteristic of cancer; promptly healed completely*; end-result unknown. Lèvêque Lasource in noting that cancer may be happily terminated by gangrene or a "fonte putride," regarded Richerand's case as more remarkable than the above example. (444, pp. 28-29; 583k)

9. (*Richerand*): Female, aged about 48, very hard carcinoma right breast, untreated; admitted to St. Louis Hospital, Paris; *violent inflammation, then gangrene set in; lancinating pain during necrosis; whole tumor mass detached itself from chest wall, with enormous eschar, leaving healthy ulcer which healed in less than two months.* End-result unknown. (438; 444; 701, pp. 516-517; 851; 856; 911) Vautier, in citing this case,

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discussed whether or not cancer is cured "by the sole forces of nature." (892) He stated he had "found several cases in searching the writings of the most careful observers in which cancer is terminated happily by gangrene." He also cited "a more recent case in which an old woman developed an acute concurrent adynamic fever which cured her completely." He noted Pouteau's opinion that cancer may be cured by resolute (alterant) treatment. To confirm this view, Pouteau had reported the case of a woman who was cured by the appearance of an ulcer on her leg. Shortly after the ulcer cicatrized the cancer recurred. Then they established an issue at the site of the former ulcer and the cancer soon disappeared a second time. (This sounds like Schwencke's case, abstracted in Series D, case 1).

10. (*Garneri*): Female, aged about 50; extensive cancer involving entire left breast, 18 months' duration; unbearable lancinating pains; travelled 10 leagues to physician, then developed "*putrid, low-grade fever; during entire duration of fever, patient does not remember having felt her cancer*"; pain returned on 15th or 16th day, worse than ever; inflammation developed, then gangrene entirely destroyed the neoplastic tissue by 25th day; ulcer cleaned up, healing complete by 56th day; "*patient returned home cured*"; end-result unknown. (278; 583k; 851)

Bayle and Cayol cited the above "remarkable example" and added that "gangrene could, rarely, become a means of cure in cancer of the breast" and that "they had seen the entire tumor slough off by the action of the gangrene. The wound resulting from this separation then heals in a short time." (22) These authors regarded as of even rarer occurrence than gangrene the cases of advanced cancer in which complete regression occurred without ulceration or surgical intervention. They cited Nicod's case and stated that they had personally observed several cases. Most of these neoplasms were of special structure: dry and hard as cartilage; having reached a certain size they shrivelled up. The overlying skin became wrinkled, forming crevasses, the nipple being deeply retracted; at this step the ulceration, if it exists, may dry up and heal. While this occurs the patient feels internal pain (more or less violent), a sort of constriction of the chest and profound general malaise. Nevertheless, the tumor is only slightly or not at all painful. *There is usually a fever of a bad character, which ends by causing the death of the patient.*" (22)

11. (*Cruveilhier*): Female adult; type and site of cancer not recorded; developed gangrene; complete sloughing of growth, radical cure; end-result unknown. (171, Vol. 1, pp. 122-128; 911)

12. (*Cruveilhier*): Female adult; type and site of tumor not recorded; gangrene developed; death occurred as a result, with symptoms of adynamia. (171, vol. 2, pp. 122-128, 911)

13. (*Cruveilhier*): Female adult; tumors of unknown origin all along thigh; all successively sloughed out as a result of gangrene; "complete cure"; end-result not recorded. (171, Vol. 1, pp. 122-128; 911)

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14. (*Boyer*): Female adult; very extensive inoperable cancer left breast; weak and cachectic; while "taking the waters" at Barège, *gangrene developed, involving entire neoplasm, which sloughed off; very extensive wound healed completely*; large number of recurrent nodules soon developed in scar; disease progressed; death 8 months later. (64, Vol. VII, p. 234; 70, p. 259; 583k)

15. (*Abernethy*): Age and sex not given; prior to 1830; enormous round cell sarcoma; lymphadenopathy in left groin; *inflammation and ulceration developed; tumor became progressively more gangrenous until entire growth was destroyed; area healed*; end-result unknown. (1, Vol. I, p. 37; cited by Broca, 1866, Vol. 1, p. 238).

16. (*Dupuytren*): Female, aged 40; extensive scirrhus carcinoma breast; operation refused; 18 months later patient bedridden, cachectic, affected breast voluminous, crepitant to touch, as if air was circulating in it (gas gangrene?); shortly before this inflammation had developed, fever, frequent emesis for 48 hours; Dupuytren thought *gangrene had developed in deeper portions during this inflammation*; 3 incisions made, large quantity viscous fluid evacuated; volume, tension decreased (patient had been almost moribund); breast dressed with chlorinated compresses; 8 days later again seen, better; *large portion breast gangrenous; blackened, swollen, necrotic pieces emerged from incision*; no septic poisoning; breast had reduced $\frac{1}{3}$; necrotic portions cut off; other portions detached themselves soon after; *no trace of growth 4 weeks after gangrene set in*; considered cured; end-result unknown. (218; 583k; 851, case 54)

Comment: Vautier in citing this case mentioned another advanced breast cancer patient who was being treated with hemlock and other remedies when she developed a severe erysipelas with suppuration, lasting 7 or 8 days, resulting in cure. Three times thereafter there were slight symptoms of recurrence (pain, etc.), which were dissipated by the application of leeches. (892)

17. (*Dupuytren*): Age and sex, type and site of tumor were not recorded; *following the development of gangrene there was complete separation of tumor from surrounding soft parts, which then healed in the manner of simple wounds; "complete cure"*; end-result unknown. Dupuytren stated that gangrene rarely involves malignant tumors; he observed only two cases in which complete cure was produced in this manner, but he "had very often seen gangrene only partially destroy a cancerous mass, and thus exercise no beneficial influence on prognosis. This variation in results had hitherto not been explained." (218) Dupuytren attributed it to "whether the gangrene develops in a noncircumscribed tumor or in an encapsulated growth. In the former, gangrene causes only partial destruction and the patient will not be cured while in the latter, the gangrene will more easily destroy the entire tumor which is enclosed in a fibrous wall, and in these cases the patients may be completely cured." (218)

SERIES G, INOPERABLE CANCER, GANGRENE

18. (*Fristo*): Mme. A., female, aged about 60; enormous inoperable ulcerated cancer breast, axillary lymph nodes; repulsive odor from ulceration; solution calcium chloride applied to correct the odor; *skin and cancer tissue of breast and axilla became gangrenous; ulcer became healthier, soon covered with healthy granulations, flattened down forming solid, very extensive cicatrix* in concentric rings, adherent to all neighboring tissues; traced well, free from recurrence few months later; end-result unknown. (70, Vol. 1, p. 250; 269, p. 40; 851, case 53; 583k)

19. (*Jackson*): Female, aged 70 to 80; scirrhus tumor breast, of 40 years' duration, of almost stony hardness, very movable, apparently encysted in character (operation delayed due to age of patient); *tumor ulcerated, then sloughed away piecemeal until whole tumor was discharged*; wound healed kindly, leaving patient in perfect health. (912)

20. (*Hébert*): Male adult; lipoma left shoulder, size of egg, traumatized due to occupation; hospitalized; *gangrenous eschar formed, very inflamed, suppuration*; area poulticed; eschar sloughed off; remains of tumor excised; end-result unknown. (70, p. 253, 324, p. 17)

21. (*Paget*): Female, aged 47; recurrent "fibroma" mammary region; *tumor and surrounding tissues became gangrenous; shortly thereafter whole tumor sloughed off leaving huge cavity*; as sloughing cleared, hard recurrent nodules appeared; disease progressed causing death 2 months later; autopsy showed 20 or 30 metastatic lesions in lungs, ulcer nearly 30 cm. wide in mammary region. (70; 583k; 625, pp. 409-41)

22. (*Paget*): Female, aged 14, prior to 1853; very extensive chondroma of tibia (had grown to 60 cm. in circumference in 18 months); *gangrenous inflammation developed after simple incision, necessitating amputation at thigh*; end-result not recorded. (70, p. 253; 625)

Undoubtedly the 22 cases cited above which were observed between 1742 and about 1860 had many organisms in their ulcerated, advanced cancers, and some of these may have helped produce the dramatic and rapid necrosis and sloughing observed, possibly through stimulation or release of tumor necrosis factor or interferon.

In contrast to all the above cases in which gangrene developed in or near the tumor, the following case may be cited as an example of a case with gas gangrene infection occurring elsewhere.

(*Wyman*): male, aged 65; untreated anaplastic spheroidal cell carcinoma of colon; onset, September 1947, pain in left lower abdomen, weight loss, difficulty in defecating; onset of symptoms occurred a few days after all his teeth were extracted; November 10, 1947, became febrile (102°F.); blood cultures grew *Clostridium Welchii*; *necrotic area in mid-thigh*; November 19, 1947, incision, aspiration of foul-smelling, greyish

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brown pus and gas from 2 areas; penicillin, sulfamezathine and anti-gas gangrene serum given; general condition improved, but infection extended down leg causing death December 2, 1947, 3 months after onset. Autopsy showed carcinoma of descending colon extending around 75% of bowel (constricting but not occluding) it was adherent to psoas sheath, contents of which were gangrenous; superficial tissues over Poupart's ligament were also necrotic. Growth had eroded through all layers of gut wall; muscle showed much edema and hyaline degeneration; C1. Welchii were present in spleen. (950)

SERIES H, MALARIA OR SYPHILIS INOCULATED

1. Malaria

As reviewed in the Introduction, there have been a number of reports concerning the possible antagonism between malaria and cancer (69, 182, 331, 463, 557, 618, 741, 742, 743). Six case histories are included in Series B, Group 2, indeterminate (not traced five years, or without microscopic confirmation of diagnosis). These patients all developed malaria accidentally.

At least three physicians are known to have attempted to induce malaria in cancer patients and nine cases were reported. These are listed in the following table. Braunstein reported six of these cases in 1931. He stated that with almost all his patients, enlargement of the spleen and marked reactions in the tumor were apparent before the onset of malaria. In the cases of external growths there was hyperemia, swelling and pain. In the cases of carcinoma of the liver and the rectum the patients complained of pain and tension in the tumor area. With onset of the fever the local symptoms increased. Immediately marked necrosis of tumor tissue occurred. When the local reactions and the fever decreased, temporary but marked regressions of the tumor were observed.

He concluded that both clinical and experimental observations indicate that cancer can be treated with malaria, but this method should be considered as palliative therapy which produces only temporary results. He believed that not only did malaria stimulate the reticuloendothelial system, but it was partly specific in its effect.

He advocated the use of malaria in the early stages of the disease, not in advanced or metastatic cancer, where the patient "is no longer able to produce enough defensive material through his own R E S."

Other investigators discounted that there was any antagonism between malaria and cancer (158, 412, 588, 688, 732, 782, 823).

Quite recently Dalldorf and his associates working in Kenya on the etiology of Burkitt's lymphoma pointed out that "the effects of malaria, particularly chronic malaria, fall principally on the reticuloendothelial system," and they emphasized the similarity between the distribution of holoendemic malaria and Burkitt's lymphoma (180). Thus the R E S in young children in these areas receives repeated insults and at necropsy, whatever the cause of death, contains much malarial pigment (82a).

It is possible that where acute malaria developed and was controlled by quinine, a beneficial effect in concurrent cancer might be observed, whereas in certain areas such as parts of tropical Africa and New Guinea where malaria is highly endemic, intractable and ineradicable, occurring in very young children, that these children may be more susceptible to Burkitt's lymphoma than children who have not suffered from chronic malaria.

This is one more instance of the fact that chronic infections rarely had a salutary effect on cancer patients.

SERIES H: INDUCED MALARIA IN CANCER PATIENTS

Physician References	Diagnosis	Malaria Injections	Onset of Fever	Immediate or Final Result
1. Rovighi 741; 742	inoperable carcinoma of rectum	inoculations of blood from tertian malaria	very severe attacks fever, not quite controlled by quinine	disease progressed, cachexia, death few months later
2. Nocht 467, p. 337; 583K	mammary carcinoma, many metastases, especially in brain, seen at autopsy	inoculations of blood from tertian malaria; Plasmodium falciparum found in blood	typical febrile attacks, profound prostration	death shortly after malaria developed
3. Nocht 463; 467, p. 337;	carcinoma of stomach	inoculations of blood from tertian malaria; Plasmodium falciparum found in blood	malaria induced, caused profound prostration	death shortly thereafter of cachexia
4. Braunstein 69	carcinoma of lower lip and palate	inoculation June 14, 1929	1 week after injection marked splenomegaly, severe pains, hyperemia, hemorrhages in tumor; after 11 days necrosis and ulceration of tumor surface; onset of fever 12 days after inoculation	after 4 days malaria attacks, tumor smaller, central necrosis present; end result unknown
5. Braunstein 69	carcinoma of throat and larynx	inoculation July 2, 1929	7 days after injection severe pains in tumor and left arm	after 3 malarial attacks, necrosis and regression of tumor apparent; spleen not palpable but was "hurting"; end result unknown
6. Braunstein 69	hepatoma confirmed after exploratory laparotomy	inoculation July 4, 1929	7 days after injection splenomegaly, severe pains in tumor	after 8 febrile attacks (to 41.8°C.) pain ceased, tumor regressed, no ascites, temperature normal; end result unknown

7. Braunstein 69	carcinoma of descending colon and sigmoid	inoculation February 11, 1930	13 days after injection 1st fever	after 4 malarial attacks splenomegaly, cessation of pain, temporary decrease in size of tumor; end result unknown
8. Braunstein 69, 583K	mammary carcinoma with axillary involvement	inoculation March 17, 1930	5 days after injection 1st fever	marked reaction in tumor, spleen slightly enlarged after injection, end result unknown
9. Braunstein 69	carcinoma of rectum with liver metastases	inoculation May 28, 1930	13 days after injection 1st fever	very marked reaction and hemorrhages in tumor; end result unknown

SERIES H, MALARIA OR SYPHILIS INOCULATED

2. Syphilis

As noted in the Introduction (pp. 6-7) a small number of physicians in France and Italy became interested in the possible beneficial effect of syphilis on cancer patients. Their interest was aroused by Didot's long report (1851) entitled "The prophylaxis of cancer by artificial syphilization." (202)

In presenting this before the Belgian Medical Academy in Brussels, Didot stated that the idea rested on a series of incontestable facts which indicated that there was an antagonism between syphilis and cancer. He believed that he was the first to suggest the therapeutic application of this antagonism. He stated:

The treatment of cancer has not progressed one step, and will not do so, as long as one limits one's approach to removing the exterior manifestations of the disease without affecting the general diathesis of the entire organism:

To do this one must find a natural or artificial antagonism to balance or neutralize the pathological influence. (202)

Didot believed that cancer was caused by a virus—and that if this hypothesis were true, then this virus must have its antipathies, repulsions and antagonisms. He studied this problem and found syphilis presented definite antagonistic characteristics for cancer. He then outlined some of his findings:

Sex: Cancer occurred 30 to 50 percent more frequently in women than in men, with an enormous predisposition for the female reproductive organs. Didot stated that there were far more male than female syphilitics in France, and there were two female cancer patients for every male cancer patient. He noted that these female cancer patients had not contracted syphilis. He reiterated, "Syphilis ne marche pas avec le cancer." He added that if one studies the prior health of cancer patients one notes that since the time of Hippocrates their previous health has been good until onset of the cancer.

Organs affected: A very large percentage involved the digestive tract (426 out of a total of 918 studied). Except for the mouth and anus, the proportion of syphilitic lesions involving the g.i. tract was slight. There were 234 cases involving the genital organs in women (25 percent) and only 23 involving the male genitals. He believed this showed a remarkable immunity of the male organs to cancer and noted that men are much more frequently infected with syphilis. He admitted that males who had had syphilis had been known to develop cancer but suggested that in such cases the infection had been arrested locally by cauterization before it spread throughout the body, and had, therefore, not affected the constitution.

Incidence according to occupation: Didot noted that uterine cancer occurred more frequently among the leisure class, virgins, sterile married women, sedentary women, those subject to abundant leukorrhea or melancholia or surrounded by all luxuries—a rather wide latitude which had but one exception: the rarity of cancer of the uterus among prostitutes as cited by Lebert and others.

In India where cholera, small pox and syphilis are more prevalent there had been

SERIES H, MALARIA OR SYPHILIS INOCULATED

only one case of cancer of the uterus admitted to the Calcutta Hospital in a three-year period according to Lebert.

Didot noted that the men of India, Egypt, Senegal and other tropical areas seemed to have only slight, inoffensive symptoms when they developed syphilis. He attributed this to the warm climate, abundant sweating and vegetarian diet.

As to occupations, Didot reported that while prostitutes were immune, laundresses were very apt to have uterine cancer. Lebert found that seven out of 29 of his cases were laundresses, and Joly found the majority of his uterine cases were laundresses. He offered no real explanation for this, but suggested that "perhaps these laundresses become infected with a cancer virus in pursuing their work." (202)

Syphilization: Didot recognized that in suggesting the artificial production of syphilis as a means of combating cancer, he might be criticized for introducing a "shameful disease." He replied: "The secrets of nature have nothing immoral or shameful . . . and it is always possible to control syphilis, but cancer inevitably kills, when one fails to neutralize its early manifestations." (202)

Didot then described the experiments of Auzias Turenne of Paris and Casimir Serino in Italy on this problem.

Turenne vaccinated monkeys, cats and marmots with syphilis and found that after repeated inoculations they became immune to all syphilitic infection. A young German professor, Robert de Wetz, of the University of Wurzburg, then consented because of his devotion to science to allow Turenne to inoculate in four different areas on his arms the pus from the chancres which had been produced in these animals. These inoculations all "took" and the brave young man allowed them to spread on his arms for 10 days. Ricord states these were not dangerous and would not cause constitutional syphilis—that they were *pseudo-chancres* because there had been no evidence of *specific induration*.

At this time Sperino, an Italian surgeon in Turin, inoculated 52 female syphilitic patients on his venereal service. These patients were given inoculations of pus from a primary syphilitic ulcer, and they all were cases of primary or secondary syphilis. The inoculations were made in two or three different places on the abdomen with a lancet, and they were repeated once or sometimes twice a week. The sites of inoculation were immediately covered with adhesive tape to keep the pus in contact with the wound. Each time the pus was obtained from a fresh ulcer from the patient herself or from some other woman if her own ulcers were old, chronic and not capable of inducing a fresh one.

Three days after inoculation (rarely on the fourth day), a syphilitic pustule would appear, and at once a typical primary ulcer would develop, with all its characteristics. In every case the first ulcers thus produced were larger, deeper, discharged more pus and lasted longer, leaving larger scars than those subsequently induced. Each successive ulcer became smaller, less inflamed, less painful, more superficial and finally after about 8 or 10 inoculations (3 sites each), one noted only a little pustule which healed up in 5 or 6 days. Thereafter, the inoculations no longer produced any effect, even though repeated several times with pus obtained from other patients infected with recent ulcers which produced large deep ulcers on patients in the early stages of inoculation therapy.

SERIES H, MALARIA OR SYPHILIS INOCULATED

The above description applied to results obtained with patients having been recently affected with syphilis. In patients who had had the disease for many months or years, with chronic extensive ulcers, in which the entire organism was saturated with the syphilitic spirochetes, in these cases the first artificially produced ulcers were small, and after a few inoculations, no further ulcers were produced.

The only treatment given was a few baths, local applications of refreshing ointments, the artificial ulcers healed up and the general health was perfect. Therefore, they concluded that the inoculation of the "syphilitic virus" could be useful in curing primary or constitutional syphilis. All the primary ulcers that were recent and not too large healed up in a few days after the appearance of the artificial ulcers, and the more extensive chronic indurated lesions of 2-4 years duration, which had been refractory to mercurial and iodide treatment, as well as to repeated cauterization with silver azotate, and other chemicals, all these also rapidly improved and progressively healed, after a few inoculations of the virulent pus from a fresh ulcer obtained from another patient. The most ancient and the deepest inguinal ulcers were also cured as promptly after inoculation. Lesions of the mucous membranes also promptly faded away, including one vast ulcer on the posterior aspect of the pharynx, which was cured after the third inoculation, as well as a "serpiginous ulcer of the right knee in a woman who also suffered frontal headaches (the latter equally calmed).

Didot did not pretend to understand how these beneficial effects were produced, but he pointed out that "we do not know any more of the mechanism involved in vaccination for small pox, nor how quinine cures malaria, nor mercury syphilis." (202)

He was certain, however, that all these women that were saturated with the syphilitic virus for five months *were without a single exception* no longer subject to constitutional syphilis. He watched their general health improve after the acute period of the artificial ulcers had passed. As to whether the cure was permanent or not, only time would determine, he added.

Turenne explained *syphilization* in a letter to the Union Médicale of Paris (August 22, 1851). During that year, Ricord was much opposed to Turenne's theories. Didot suggested that it was unnecessary to wait until these investigators settled their differences or fully understood the mode of action in this phenomenon. He said is it not odd to outlaw a salutary method, because we do not understand its physiological effect? (He cited malaria and quinine as an example and said let the same follow for syphilization, since no unpleasant or serious complications had followed its experimental trial.)

The first to suggest the inoculation of syphilis in incurable cancer appears to have been Latour (1850), as cited by Didot, although Thiry tried to pretend he had been the first.

Application of syphilization to cancer: Didot believed that "the syphilis spirochete was antagonistic to the cancerous virus. How best to use this? He discussed two possible methods: a) *Simple artificial inoculation*, b) *Syphilization*, as practiced by Turenne and Sperino.

Richerand is quoted as being one of the first to observe that cancer avoids syphilitics when he stated: "All prostitutes who do not contract venereal disease succumb to cancer of the uterus."

SERIES H, MALARIA OR SYPHILIS INOCULATED

Didot believed that the second method would be absolutely useless—that one must induce a real syphilis infection, not immunize a patient *against* syphilis.

Practical indications: He suggested inoculating syphilis as soon as there was microscopic proof of cancer and even in doubtful cases. As to how far one should let such induced syphilitic infections progress, he was a little vague. He suggested, however, that it was better to continue it than to stop it too soon. He suggested using the pus from a recent primary chancre in the "specific period," or even while indurated—remembering however that indurated chancres very soon lose their ability to produce inoculable pus." He advocated a single inoculation of this pus with a lancet on the abdomen, spreading it over the wound, and covering the area with adhesive tape. If the first inoculation doesn't take, one must repeat them a certain number of times, with fresh material, until one obtains a specific induration, or secondary lesions are apparent.

Patients and their families must be clearly told of the entire experimental procedure; that is, the grave prognosis of the cancer, the proposed treatment, and their free consent obtained. Thus Didot outlined his proposed treatment although he had not yet tried it on any patients. He appealed to the impartial spirit of the clinicians and research workers, and urged them seriously to consider the general principles on which this work was based. He was sure that it contained a truth which had not yet been understood. In conclusion he stated with Victor Van den Broeck: "Quand une grande idée vient à jaillir du sein du chaos, quoi que fassent la routine, l'ignorance et la mauvaise foi, le génie protecteur de la vérité le maintient en quelque sorte à l'abri des outrages de l'erreur, jusqu'au moment où d'opprimée qu'elle était, elle devient à son tour dominante."*

The discussion of this paper was acrimonious and lasted for two different sessions. Ricord took part and vehemently asserted that it was illogical to produce syphilis in a cancer patient. Didot asked, in reply, if there existed any other means to combat generalized cancer. "Since we are absolutely helpless in the presence of advanced cancer, it is fair to consider that all means are good, if they offer a less dangerous prognosis than cancer itself. What have we to lose—the cancer patient is doomed to die—and therefore it seems perfectly rational to invoke the powerful intervention of syphilis to defend the organism against the attacks of cancer." (202)

The discussion became very prolonged and critical. Finally Didot recapitulated his findings. This episode is a very good example of the tragic discouragements, insults and blame which came to those who dared to propose new or radical approaches to the control or cure of cancer.

Only one physician, Seutin, dared to encourage Didot and Thiry, stating: "In the presence of a disease which, up to now is without remedy, one can, it would seem, praise these men for the experiments they wish to undertake. It is easy to say to these patients, 'Do nothing, go to the country, go to the spas.' . . . The arguments of our illustrious

*English translation: "When a great idea bursts forth from the breast of chaos, despite all that routine, ignorance and duplicity can do, the supreme protector of truth shelters it somehow from the damaging effects of false doctrines until the moment when, from being slandered, it becomes in turn, predominant."

SERIES H, MALARIA OR SYPHILIS INOCULATED

colleague, Ricord, would tend to diminish the zeal of these investigators. Therefore, I say we can, without danger, substitute for a fatal disease, another disease." (202, p. 647)

Unfortunately, these vitriolic criticisms did apparently block further research along these lines and we only found two case histories to include here, i.e. apparently no one after Auzias-Turenne attempted to utilize syphilis as a means of increasing host resistance to cancer.

Brief Abstracts

1. (*Auzias-Turenne*): Female, aged 40; hard nodular mammary cancer, lancinating pain, untreated; a grandparent, mother, uncle and aunt had all died of cancer. Inoculations of the matter from syphilitic chancres were made on the back of the neck; two or three chancres were produced and became indurated; a macular erythema soon appeared and other symptoms of constitutional syphilis developed successively for 1 year, during which time the breast cancer diminished, pain ceased; then mercurial ointment was instituted to arrest the syphilis; patient recovered; in good health 2 years after onset. (201; 202; 583k)

2. (*Alquié*): H.P., male, aged 72; recurrent inoperable cancer lower lip; (onset 1846): growth stationary then very rapid following trauma; surgical removal; recurrence; general condition affected; by January 1851 ulcerated growth involved half lower lip, both inside and outside mouth (4×6.5 cm.); given arsenate of iron, conium, opium; tumor increased 25%; local treatment consisted of dressings covered with cerate; January 13, 1951: compress soaked with pus from very active 18-day-old chancre was applied to the tumor; 5 days later a small incision was made in the ulcer using scalpel covered with chancrous pus from same syphilitic patient; that night considerable fever, ulcer and all fungosities of tumor were inflamed; local and general condition rather alarming; improvement evident 2 days later when ulcer presented all characteristics of syphilitic chancre; *thereafter very rapid regression; suppuration; in 10 days growth decreased 50%; general condition improved; healing took place*; improvement ceased February 4, 1851; in three weeks fungating nodules size of small apple; case then reported so end-result unknown. (10; 943)

Auzias-Turenne treated several other cases by inoculation of syphilis, but obtained only superficial chancres which did not become indurated and he had to cope with two cases of phagodena. He stated that *these cancer patients seemed to be immune to syphilis*; he emphasized that if one wished to induce syphilis in cancer patients, one should not wait too long and should *not* do so if the case was in the terminal stages. At the time of his report he was treating several inoperable cases; many had had operations but were beyond further surgical intervention. In none of these was any unfavorable complication produced, while in most a notable amelioration occurred following the inoculations. He ceased the latter when he had produced constitutional syphilis. When the syphilis had become well-established he controlled and destroyed it by "syphilization"—i.e. repeated small injections. He believed that the syphilis could also be controlled by mercury, and in any event that these inoculations did not expose the cancer patients

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to any danger. He added: "This is a new road to explore. One can do so without inconvenience for the patient and thereby one may make useful discoveries." Auzias-Turenne's report caused severe criticism in the medical press of Belgium. (202, discussion, pp. 337-353, 61-649)

SERIES I: HODGKIN'S DISEASE WITH CONCURRENT INFECTION (3 STREPTOCOCCAL, 1 TUBERCULOSIS, 1 MEASLES WITH FEVER TO 105°F.)

Although many physicians have observed cases of Hodgkin's disease apparently benefited by concurrent infections very few have reported them, hence we have found only five, and only one of these was published.

1. (*Elting & Coley*): C.A.T., male, aged 38; onset Hodgkin's disease 1905; cervical nodes excised; recurred; 2nd operation, again recurred; x-ray; masses in neck, axillae increased; extensive dissection rt. cervical nodes; 2 wks. later nodes rt. submaxillary triangle and rt. axilla removed; *severe streptococcal infection neck wound, general pyemia, numerous abscesses; complete recovery, no further recurrence*; died heart failure 1938. (80; 123; 142, case 4, p. 655)

32 yrs.

2. (*Craver*): I.K., male, aged 38; onset Hodgkin's disease April 1926; cervical node excised; *concurrent tuberculosis* with cavity formation; x-ray (1 to neck), May 1926, 1 more April 1927; *tuberculosis required hospitalization intermittently for several years*; April 1933, mass in iliac fossa; x-ray (1200 r) caused regression; Herpes zoster on lt. chest; bedridden April 1935; another x-ray treatment November 1935 to neck, and to keloid on chest wall (this subsided); as Hodgkin's disease progressed, further x-ray given, final course 1937 (no improvement; death June 1938. (528)

over 14
yrs.

3. (*Cappell*): G. McC., male, aged 39; onset Hodgkin's disease July 1928; node in lt. axilla enlarged; by October several enlarged there, above and below lt. clavicle; these were removed surgically; October 1928 deep x-ray to neck and axilla; January 1929, severe cut to lt. index finger; *abscess* beneath lt. pectoral muscle at site of previous surgery: (*hemolytic streptococci*); *erysipelas in surrounding area, fever to 4°F.*; prophylactic x-ray to neck, axillae, groin, mediastinum, spleen and mesenteric lymph nodes (half an erythema dose given in small fractions); w.b.c. fell from 7,000 to 5,000 with no upset in general health; no lymphadenopathy present; general condition excellent July 1929 to March 1930, resumed full duties as pathologist; then began to feel "seedy"; slight temperature 100°-101°F.; sent to country May 1; fever continued occasionally reaching 103°F. until the end of June when it fell to 99°-99.4°F.; felt much better; returned to work July 1930; blood count normal August 1930, *herpes infection* at site of abscess; some neuralgic pain in lt. shoulder; temperature 100°-101°F., later to 103° or 104°F., with profuse sweating temperature fell abruptly to normal by late August; patient surprisingly fit. No nodes were palpable; periodic

SERIES I: HODGKIN'S DISEASE WITH INFECTIONS

x-ray examination revealed no mediastinal involvement; further bouts of severe pyrexia occurred in January and February 1931 lasting 2-3 wks., leaving him exhausted; death occurred in late 1931 or early 1932 following a prolonged bout of fever. (123; 589)

3½ yrs.

4. (*Henry*): male, aged 40; Hodgkin's disease involving the cervical axillary and inguinal nodes; moderately severe scarlet fever; *all symptoms of Hodgkin's including the lymphadenopathy disappeared; apparent cure; end result unknown.* (325)

5. (*Miller & Southam*): A.K., male, aged 11; had been sickly for 6 yrs., frequent respiratory infections, easily fatigued, subnormal weight gain; diagnosed December 1949; enlarged iliac and para-aortic nodes found at laparotomy; January 1950 bilateral large inguinal lymph nodes, small cervical and axillary nodes, 2.5 cm. rt. hilar mass, questionable hepatomegaly; HN₂, also x-ray to groins; adenopathy persisted during 1950, also back pain, fever, splenomegaly; ACTH, more HN₂, transient improvement; also had painful erythematous nodules on legs; biopsy: eosinophilic reaction not typical of erythema nodosum; disease progressed 1951, more extensive lymphadenopathy, destructive bone lesions in mandible, elbow and heel; mediastinal enlargement, increasing fever, weakness, bone pain, cough; x-ray and T.E.M., little response; February 1952 (26 mos. after diagnosis): *measles, fever to 105° F. for 2 wks., then promptly became afebrile, adenopathy completely regressed; hemoglobin increased from 10 gm. to 13 gm. %; appetite improved, gained 10 lbs. in 2 mos.; no further evidence Hodgkin's disease;* became active in sports, part-time jobs in school, then worked as a mechanic; married about 1963; adopted a child; laparotomy 1964 for another reason: no lymph nodes were found to biopsy; wife left him about 1970; he remained well except for cellulitis of his thighs associated with lymphedema; by 1980 there was also troublesome edema of the scrotum. (589)

31 yrs.

SUMMARY AND CONCLUSIONS

In reviewing these observations of over 500 physicians in the past 200 years indicating the possible beneficial effects of various types of acute infections on neoplastic disease, one must remember that most of the cases were observed before the development of bacteriology, antibiotics or present day efficient follow-up clinics. It is therefore not surprising that only 47 inoperable or far advanced cancer patients who developed concurrent infections are known to have had permanent complete regressions (traced from 5 to 48 years after onset). Another 70 cases of operable cancer who developed infections before or after surgery, remained free from further evidence of disease from 5 to 54 years after onset. This group of cases emphasizes the importance of adjuvant toxin therapy before or after operation to lessen the chance of recurrence or metastases.

It would now appear that in many of the cases in which only incomplete regression occurred following infection, that if the surgeon had excised the remains of the growth or applied "setons" to prolong the effect upon the patient, a larger number of permanent results would have been obtained. Examples of this type are Biedert's famous case (Series A, Group 1, Case 4) or Rigal's (Series G, Case 6).

A number of inoperable cases listed as indeterminate successes had complete regressions and were probably permanent results, but since they were followed less than five years they are listed separately.

At least 30 physicians attempted to induce a pyogenic infection in over 70 cancer patients, others inoculated syphilis and still others malaria. With one exception, these experiments occurred before there were antibiotics to control such induced salutary infections if they became too severe.

When very extensive inoperable cancer patients developed erysipelas or other severe pyogenic infections, spontaneously or by inoculation, the tumors disintegrated very rapidly producing large quantities of necrotic tissue. In some patients, this appeared to cause toxemia which proved fatal. For examples, see Series A, Group 4, Case 1, and Series E, Case 29. Such patients might have been saved if the necrotic tissue had been evacuated surgically. Beck's case also clearly indicates the great need for adequate nursing care and proper nutrition in these advanced cases, in order to help them respond more effectively to the infection or whatever treatment is given. An example of what hyperalimentation could do in an inoperable metastatic case is seen in Series B, Case 33.

With the exception of Wyeth, who advocated introducing cultures of streptococci into the wounds following surgery for *operable* neoplasms see Series D, all other physicians selected inoperable or far advanced, often terminal or aged patients in whom to attempt inducing an infection. It is therefore all the more surprising that any of them recovered for we now recognize that in the late stages of the disease, immunologic responsiveness may be inadequate or entirely exhausted. Matagne is the only physician who attempted to induce erysipelas in an operable case *prior* to surgery (Series D, Case 5).

In comparing the results obtained in operable and inoperable cancer patients who

SUMMARY AND CONCLUSIONS

developed pyogenic infections with those in whom non-pyogenic infections occurred, it is evident that the pyogenic produced the great majority of dramatic and lasting regressions, as well as many more of the incomplete regressions, than occurred with the non-pyogenic types such as typhoid, malaria or tuberculosis. Streptococcal (especially erysipelas) and staphylococcal infections seemed to be implicated in the largest number of successful results. The cases grouped as Series G, with concurrent gangrene, probably include several in whom pyogenic bacteria may have started the gangrene in their tumors. Most of these were observed in the early 19th Century before asepsis was practiced and before bacteriology made it possible to distinguish clearly which organisms were responsible.

It would appear that in many of these cases of so called "gangrene," they were caused by the tumor necrosis factor recently described by Old and his associates (48a; 333a). The speed with which this factor (induced by microbial products) can produce tumor necrosis is very dramatic.

Cells of the reticuloendothelial system probably play an important role in the production of interferon (331; 331a). Many non-viral substances can induce interferon production, including bacteria, bacterial endotoxins, statoclon, phyto-hemagglutinin etc. Some such as endotoxin induce the formation of viral inhibitors with molecular characteristics differing from virus-induced interferon (331).

While it would appear that endemic cholera, dysentery and syphilis or other non-pyogenic infections may have helped to reduce the incidence of cancer in the areas where they were prevalent, these do not appear to be as significant as the pyogenic type. The data assembled here suggest that, with modern knowledge regarding the many salutary effects which certain pyogenic bacteria or their vaccines and enzymes may have on host resistance to cancer and allied diseases, a great deal more serious research at all levels is warranted now. Such studies should help us to determine how to utilize these microbial products to best advantage in all types of neoplastic disease alone or as adjuvants to surgery and/or radiation or chemotherapy. This type of combination therapy may enable surgeons to perform more conservative surgery, preserving the lymph nodes, because bacterial products can stimulate their ability to destroy neoplastic cells. The diverse physiological effects which certain microbial products are now known to produce include production of tumor necrosis factor, stimulation of the reticuloendothelial system, leukocytosis, increased phagocytic capacity of the lymphocytes and macrophages, increased production of interferon, and increased oxygenation of the tissues. Also of significance is the fact that some strains of streptococci and certain other bacteria, or their vaccines, can increase the antigenicity of tumor cells provided that they come into significant contact with the tumor.

Of special importance is the fact that an infection or bacterial endotoxins, if given first, can potentiate the response of the tumor to radiation while protecting the normal tissues against the deleterious effects of radiation. Therefore, one may administer smaller doses of radiation, thus avoiding the serious late effects of the larger doses, which is of special significance in dealing with cancer in children. The fever and acute inflammation elicited by certain bacteria or their vaccines apparently also play a salutary role, since cancer cells are known to be more sensitive to heat and to inflamma-

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tory exudates than normal tissues, and since the histamine liberated in acute inflammation activates the reticuloendothelial system. Interferon stimulation and release also is now believed to be implicated, and this may occur more readily if fever or heat is present.

Recent recognition of the role of iron as a possibly important regulatory factor in the balance of host resistance to cancer has added a clearer understanding as to why cancer patients may be markedly benefited by developing a concurrent bacterial infections or receiving bacterial vaccines. A fine balance seems to have been evolved through thousands of years between such infections, fever, iron deficiency, immune function and tumor cell growth. This balance was upset beginning 100 years ago with the control of infections and infectious diseases, and the use of iron supplements.

One may ask why so little has been done on this approach to the cancer problem in the last 40 years. It would seem that lack of accessible data, the concentration on screening for cytotoxic chemotherapeutic agents which might control cancer as the antibiotics have controlled infections, and finally the publication of a few negative inaccurate reports by a powerful cancer organization in the United States, were responsible for discouraging all but a few investigators from entering the field. Because there seemed a need to determine the possibilities and limitations of the immunologic approach to the cancer problem, the New York Cancer Research Institute was founded in 1953, before the medical profession had shown any interest in this approach. Due to the international scope of its program, the name was changed to Cancer Research Institute in 1973.

The present study comprises all the data available on the effect of various infections on cancer. In addition of these data, during the past 27 years end-result studies of various types of cancer treated by bacterial toxin therapy have been made. Some of these have been published, others are in press (256-260; 542b; 583-583K, 592; 650-652).

A number of highly qualified investigators have begun to evaluate the effects of bacterial infections or microbial products on cancer at both the experimental and clinical level. Present indications suggest that a number of microbial extracts will eventually be available for clinical trial under F.D.A. regulations. These include purified extracts made by sophisticated modern microbiological techniques. For the treatment of advanced or widespread disease, it still may be advantageous to utilize pyrogenic preparations. It would seem that a great deal of coordinated clinical, as well as experimental, research is now warranted on various aspects of this most hopeful approach to the cancer problem.

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(With additions there are 1032 references)

Goodwin of Los Angeles reported a case of metastatic testicular cancer with regression following a severe wound infection:

"...a young man who had a testis tumor an embryonal carcinoma: when I explored him, I found a metastasis as big as my fist over the vena cava, which I took out and really didn't try to take out all the rest of his lymph nodes because I thought it was futile. He then disappeared and I thought he was dead, but during the immediate postoperative period he developed a very, very severe wound infection with staphylococcus and drained the wound infection for a long time. About five years later he howed up for a follow-up examination. I was astonished to see him still alive. It could be, of course, that I goe the only metastatis that there was but it seemed to me highly unlikely, and I always thought that the episode of infection that he had may have had something to do with it." (Letter to H.C. Nauts 6/7/1973.)

DIAGNOSIS: Congenital mixed cell sarcoma (malignant mesenchymoma) of the right thigh, confirmed by microscopic examination after biopsy at the Children's Hospital, Beijing, China. The case was completely inoperable.

Previous History: Male infant. The child had a mass the size of an apricot at birth. At seven months it had increased to 20 x 15 x 7 cm. in size. He was then admitted to the Beijing Children's Hospital.

Surgery: An incisional biopsy was performed in September 1981.

Postoperative Infection and Fever: A severe staphylococcus infection developed in the wound with abscesses in and around the tumor and high fever (39-40° C.) lasting over a month.

Chemotherapy: Endoxan and vincristine were administered once a week during the infection, as well as an antibiotic.

Clinical Course: The tumor regressed rapidly.

Further Surgery: On February 2, 1982 the remains of the tumor was excised. The pathologist reported that the whole tumor had become a benign mesenchymoma.

Clinical Course: The child remained free from recurrence and in excellent health when last traced in September 1983 over 2½ years after onset.

Reference: Cancer Research Institute Records: Personal communications from Dr. Guo Zheren, Beijing Children's Hospital, 1982-1984.



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