EFFECTS
OF CONCURRENT INFECTIONS
AND THEIR TOXINS
ON THE COURSE OF LEUKEMIA

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Of all the recorded cases of so-called "spontaneous" regression in cancer or "spontaneous" remission in leukemia, the great majority have occurred in patients who developed an acute concurrent infection, inflammation or fever, principally streptococcal infections.

Before studying this phenomenon in leukemia, approximately 350 histories of cases of malignant tumors in which such complications may have played a salutary role were assembled for study. In 167 of these patients (152 inoperable, 15 operable, untreated) the neoplasms disappeared, and 62 of these remained free from recurrence or metastases when last traced 5 to 44 years later. Among the 73 determinate operable cases in which infection or inflammation developed before or after surgical removal, 52 patients were traced 5 to 54 years later, free from disease. Thus for the entire group of determinate cases there were 114 patients traced five or more years after onset without evidence of disease.

However, if the infection developed following heavy radiation or if the disease was very far advanced, only temporary or partial regression of the neoplasms occurred. In a few of the 25 patients who died of the infection death occurred before any effect was evident on the neoplasm.

The beneficial effects of acute concurrent infections or fever on leukemia have also been observed by a large number of investigators. Over 70 such histories have been reported in the literature and many others have been cited briefly. Often the infection did not occur until the terminal stage of the leukemia, and this may have been one reason why permanent benefit following such infections has not been reported in cases of leukemia, although 36 patients with malignant lymphoma remained free from further evidence of disease after concurrent infection or toxin therapy.

As to how acute infections, inflammation, fever or bacterial toxin therapy may exert their apparently beneficial effects on patients with cancer or leukemia, it is known that neoplastic cells are more sensitive to heat than are normal cells. However, in addition to this factor, it appears that infections or their toxins may activate or mobilize various tissues or systems in the body which may be less active than normal in these patients.

The lymphocyte was first suggested as playing a role in resistance to neoplastic diseases by Murphy and his co-workers who, as early as 1914 were able to break down the resistance of animals to heterologous tumor transplants by destroying lymphocytes with irradiation or benzol (180). More recent investigators such as Toolan (238) using the irradiation technic of Murphy succeeded for the first time in propagating malignant human neoplasms in laboratory animals. Thus, while it was quite apparent that lymphocytes were concerned in maintaining resistance against heterologous tumors, and that irradiation destroyed both the lymphocyte and the resistance, the precise mechanism of action still remains undetermined.

The possible role of the reticulo-endothelial system (RES) in resistance to neoplastic diseases is now beginning to be considered as its function in various physiologic processes becomes more clearly defined. The RES is composed of cells scattered throughout the body which are actively phagocytic toward particulate matter, or can be stimulated to assume that function. Such elements are arranged anatomically in two ways: fixed reticulo-endothelial cells which are attached to and form an integral part of sinusoidal walls, and free reticulo-endothelial cells which are able to wander through the tissue spaces. Fixed phagocytes and potentially phagocytic elements line sinusoids of the liver, spleen, lymph nodes, suprarenal glands and the bone marrow. Free reticulo-endothelial cells multiply rapidly during periods of greater need and become phagocytic whenever particulate matter comes into direct contact with their cell membranes under conditions which make phagocytosis possible.

It is possible that the RES plays a role in disposing of carcinogens or leukemogens circulating in the blood, before they can exert their harmful effects. Its role once neoplasia have developed is not yet understood.

The acute inflammatory reaction is another important factor in the host's resistance to neoplastic diseases (229). It is significant that the histamine liberated by acute inflammation appears to be a physiological activator of the reticulo-endothelial system (116). (This is discussed in greater detail below.)

It is not surprising therefore, that many carcinogenic or leukemogenic agents have the property of depleting or inactivating lymphoid or hematopoietic tissues and the reticulo-endothelial system. Some of them may also depress the ability of the host to evoke an acute inflammatory reaction. However, acute infections or their toxins appear to stimulate these tissues and defensive functions.

Factors which may contribute to the increased incidence of leukemia: In reviewing the factors which appear to stimulate or inactivate resistance to neoplastic diseases it may be possible to elucidate the possible causes for the astounding increase in the incidence of leukemia and related malignant lymphomas in recent years. This increase has received little recognition (Kaplan) (120).

A. *Decreased Stimuli to Immune Responses.* Before infections or infectious diseases were markedly curtailed, the reticulo-endothelial and properdin systems were

repeatedly stimulated by a variety of infections and infectious diseases, from early infancy onwards. Smith (226) has presented evidence which suggests that cancer and allied diseases are still comparatively rare among the Indians of the United States, who still have a higher incidence of infections and infectious diseases.

B. *Chemotherapy and Antibiotics.* Not only have we been exposed to infinitely fewer bacteria or their toxins in the last few decades than was normal before then, but for the last dozen years, when an infection did develop, one of these agents was usually given. In addition to making it unnecessary for the natural immune responses to deal with the infection, some of these drugs may have a seriously damaging effect upon the hematopoietic system, leading to fatal aplastic anemia, or possibly to leukemia.

Marchal, et al (154), believed that certain agranulocytoses should be regarded as preleukemic states and they stressed the dangers of uncontrolled use of various new drugs which might produce agranulocytosis. They added: "The sulfonamides in particular are commonly employed, almost like aspirin and too often without being under medical supervision. The hemopathies that result may develop insidiously so that quite often patients do not clearly realize that the chemotherapy was the cause of subsequent serious panmyelophthisis." They also cited several cases of benzol poisoning preceding leukemia reported in the literature. In some of these patients a latent blood dyscrasia may have been present prior to the administration of the drugs. The following authors have cited such cases here and abroad: Brunn (21); Kohn (124); Harvey and Janeway (88); Rosenblum and Rosenblum (208); Ginsberg and Brams (77); Martin and Delauney (156); Stannard (230); B. Wood (263); H. Wood (264); Moody and Knouf (172); Cancela Freijó (27); Noufflard (189); Black and Meynell (11); Hansen and Bichel (84); Hargreaves, et al (85); Loyd (144); Lewis, et al (139); Welch, et al (257); see also Southam, et al (228, case 14), for another case of a child developing leukemia following frequent use of sulfonamides for recurring attacks of tonsillitis.

C. *Anti-convulsants:* Several investigators have reported that mesantoin, an anticonvulsant, has similar deleterious effects: Harrison, et al (86); Aird (2); England (46); Weller and Metcalfe; Forester; and Witkind and Waid (262).

D. *Anti-inflammatory drugs:* Another group of drugs which should be used with great caution are the anti-inflammatory drugs, for there is considerable evidence to indicate that the ability of an animal or patient to elicit an acute inflammatory reaction is one of the powerful inhibitors to successful transplantation of tumors or to the formation of metastases in animals or in man. Stifel and Burnheimer (231) reported the development of agranulocytosis following the administration of butazolidin. With cortisone it was possible for the first time to grow human neoplasms in animals successfully. Toolan (239—241). There is evidence to suggest that the depressing effects of cortisone on inflammation can be completely abolished by adequate choline administration (90—93). Since the inflammatory reaction seems to be an important factor in the host's resistance to cancer, it is interesting to find

that several investigators have observed that the ability to invoke such a reaction seems to be absent in most cancer patients. Southam, et al (229). Ungar (245) discussed this, having made a statistical study of all the patients admitted to a hospital in Basle, Switzerland, in a 20-year period ending about 1947. The incidence of acute infections or of acute inflammatory episodes was almost nil in the cancer group as compared to a high percentage occurring in the non-cancerous group. Other physicians have observed that when cancer patients are exposed to poison ivy or other agents which cause severe dermatitis in normal subjects, a very mild dermatitis or none at all is noted (245). The evidence suggests that in cancer patients the reticulo-endothelial system is less active than normal and requires stimulation.

Toxin therapy, concurrent infections (186), and choline (90—92, 197) appear to stimulate the host's ability to invoke acute inflammatory reactions. It may be worthwhile to study the possible effects of induced inflammation (vesication, fixation abscesses) since it is known that inflammatory exudates destroy neoplastic cells in vitro (143). It may be that the copious exudates produced by severe erysipelas infections played a salutary role in the defensive process which resulted in regression or remission of cancer or leukemia following such infections. One must also consider that the histamine liberated by the acute inflammation of erysipelas is a physiological activator of the reticulo-endothelial system (116, 69, 70).

A study was made in Germany by Forster of the incidence of neoplastic diseases among bee keepers, whose immune reactions are constantly being stimulated by exposure to the toxins of bee stings. It was found that in over 18,000 German bee keepers, there was an astonishingly low incidence of neoplastic diseases; 0.36 per thousand (55).

E. *Hormones.* The use in recent years of estrogenic hormones (in cosmetics, as medication or in animal husbandry to induce more rapid growth) may also be questioned since several investigators have shown that this agent may be leukemogenic, or carcinogenic. Lacassagne (128—130); Marchal, et al (154); Mallory, et al (151); Loeper and Mallarmé (142); Bowers (16). The hazard to industrial or agricultural workers handling these hormones or other leukemogenic substances such as benzol (151, 154), must be considered and adequate protection provided (106). The possible dangers of ingesting poultry in which an estrogenic implant has been incompletely absorbed should also be studied.

F. *Irradiation:* This is a leukemogenic agent to which the modern world is being exposed in seriously increasing amounts. A great many authors have cited the destructive action of large doses of x-ray or radium upon the hematopoietic system. Those reporting acute aplastic anemia include Jagié, et al (115); Bordier (13); Larkins (135); Faber (49); Merklen, et al (161); Martland, et al (157); Dunlap (41). Those reporting leukemia include Evans and Leucutia (47); Furth (63—68); Dunlap (41); Delarue (36); Kaplan (119, 120).

Abbatt and Lea (1) concluded from their studies that "These results are confirmatory of the leukemogenic effects of atomic explosions, of irradiation for tumors

and ankylosing spondilitis, enlargement of the thymus and thyrotoxicosis, and of prenatal irradiation previously reported." Clark (30 a) and Simpson and Hempelmann (225) concluded from their extensive studies that therapeutic radiation of infants may be an etiologic factor in thyroid cancer of children and adolescents. Its role in the production of leukemia or other tumors is less clear and awaits further data. They suggested that the practice of irradiating children on a large scale should be abandoned, particularly in the case of the thymus, for which there is meagre evidence that the treatment has any benefits. In other cases the benefit to be derived should be carefully weighed against the possible dangers. Fluoroscopy as well as therapeutic radiation should be included in such considerations. (Buschke and Parker (23).)

Mersky (162) and Schwartz and Ehrlich (221) suggested that the relative high incidence of leukemia as a terminal manifestation of polycythemia vera is not an expression of the natural history of the disease, but the result of repeated intermittent radiation generally given these patients.

Weder, et al (254) studied the influence of roentgen radiation and cortisone upon transplantability of mouse leukemia cells. They concluded that specific acquired immunity was more effective as a protective mechanism than natural innate resistance or genetic constitution.

Pelner (197) has recently analyzed the effects of radiation on host-tumor antagonism. He concluded: "A review of both old and recent work on the effect of ionizing radiations on the tumor and the host suggests that our conception of proper dosage may have to be revised. Large doses of radiation may have a salutary effect on the local tumor but a detrimental effect on the resistance of the host."

Other writers have stressed the relatively greater incidence of leukemia in radiologists: Caffaratti (25); Emile-Weil and Lacassagne (45); Jaulin (117); DeLaet (35); Reitter and Martland (205); Dunlap (41); Henshaw (95); March (152, 153); Furth (66); Ulrich (244); Peller and Pick (196); Meadors (160). March estimated from the statistics that radiologists had nine times more leukemia than other physicians. Others felt the ratio was not quite that high.

Upton and Furth (245 a) found that the occurrence of myeloid leukemia was drastically increased in Rf mice by a single dose of 350 r of x-ray. Most currently studied radiation-induced leukemias are lymphoid and thymic. The observations made in Japan among human survivors of atomic bomb radiation, indicating that a single exposure to ionizing radiation may produce a high incidence of myeloid leukemia, lend significance to Upton and Furth's similar findings in Rf mice. Among those who have reported on the increased incidence of leukemia among humans exposed to atomic radiation are Folley (52); Lange, et al (134) and Moloney (171). As early as 1942 Warren (251) noted that some of the personnel working with cyclotrons had an unstable bone marrow. He suggested that such persons should not work where they are exposed to radiation. (Warren, 1942.)

These observations and a great many more dealing with the carcinogenic effects

of radiation suggest that physicians should exert great caution in using x-rays or other forms of radiation whether for diagnosis or therapy, in order to lessen the dangers of subsequent development of leukemia. In treating leukemia or neoplasms, large doses of x-ray should be avoided, since heavy radiation appears to break down or inactivate several natural resistance factors against neoplastic diseases.

Further evidence which confirms this view is indicated by the investigations of Molomut, et al (168); Weder, et al (254) and of Toolan (238—241) who found that heterologous tumors, including human neoplasms will grow quite readily after the host has been conditioned with x-ray or cortisone. These findings corroborate the earlier work of Murphy and his group who stressed the vital role played by the lymphoid tissues in natural resistance against tuberculosis and against neoplastic diseases (180).

Viruses: Some modern investigators believe that a virus induces transformation of normal cells to leukemic cells. Kirschbaum (123) has pointed out that certain important questions relating to viral etiology remain unanswered. It is possible that latent viruses may be activated, or the host's resistance decreased, by such agents as radiation.

Psychological factors: Recent studies by Green, Young and Swisher (82 a) indicate that various types of psychic traumas (losses, separations or threats of separation) in a period of four years prior to onset of lymphoma or leukemia were found in all thirty-two women comprising their second series. These traumatic experiences included the loss of a significant person, father, mother, husband or child, menopause, either natural or surgical; and change of home. The authors concluded that these psychic traumas are of significance not only etiologically, but also in connection with exacerbations and duration of remissions in lymphoma and leukemia. An awareness of these findings by the physician is useful in the understanding and management of patients with these diseases.

Synergistic action of various leukemogenic agents: Multiple factors are capable of contributing to the production of leukemia, some of which may be capable of inducing it independently while others which are not independently leukemogenic may augment leukemogenesis. Obviously such promoting factors may be exceedingly difficult to detect.

The considerable evidence of synergistic action of various leukemogenic agents have been reported by Mayneard and Parsons (159); Loeper and Mallarmé (142); Furth and Boon (65); Kirschbaum, et al (122). For example, Furth and Boon (65) found that preirradiation of mice with 175 r enhances the susceptibility of four to six-week old mice to the leukemogenic action of small doses of methylcholanthrene. The leukemias appear earlier, and in larger numbers than in mice subjected to either of these agents alone. Later experiments revealed that 87 r was less and 350 r was more effective in enhancing susceptibility.

The work of Kirschbaum, et al (122), suggests that the various exogenous leukemogenic agents operate through a common mechanism. They found that both

x-rays and estrogenic hormones act synergistically in accelerating onset of induced leukemia by methylcholanthrene in D.B.A. mice, although the independent leukemogenic activity of estrogenic hormone was not demonstrable in these mice. They concluded that genetic factors determine susceptibility to specific leukemogens acting either independently or synergistically. The thymus was the most important locus for the synergistic effect of these three agents in accelerating onset of induced leukemia.

It would seem that many of the leukemogenic agents may depress or inactivate one or more of the tissues or systems which take part in the host's resistance to leukemia and cancer, and that acute infections or their toxins or substances which stimulate acute inflammatory reactions may stimulate them.

The available data on this phenomenon in leukemic patients have been assembled to stimulate further investigations.

The Effect of Concurrent Infections or Their Toxins on Leukemia: Richter (206), of the Charité Hospital in Berlin, Germany, seems to have been the first to discuss the effects of *erysipelas* upon leukemia. He stated that leukemia has been favorably influenced by several different concurrent infections, and that if one could prove that each acts in the same way, we could use Nature's process to formulate an effective artificial therapy. He then cited 11 cases, including one advanced myelogenous leukemia personally observed, in which the patient appeared to be markedly benefited following an acute erysipelas infection.

The other cases he noted are described briefly as follows:

Eisenlohr, 1874, an attack of typhoid fever caused shrinking of the lymphatic glands and the spleen. The leukocytes diminished to such an extent that the diagnosis of leukemia was no longer considered correct. Three weeks after recovery from typhoid fever, the leukemic status recurred (43).

Heuck, 1879, the leukocytes diminished from 400,500 to 80,000 in a case of myelogenous leukemia during an empyema. There was also significant decrease in the spleen. (An earlier attack of acute feverish arthritis had caused no change whatever in the blood picture.)

Muller, both cases developed septic fever, followed by an increase in the polymorphonuclears.

Quincke (202): Regression of leukemic symptoms during miliary tuberculosis.

Stintzing (232): A similar case, regression of leukemia symptoms with chronic tuberculosis.

Frohlich (59): (Rather uncertain diagnosis). Spleen and lymphatic glands diminished during a pleuro-pneumonia.

Kovacs (126): Leukemia symptoms disappeared during an influenza, with disappearance of large mononuclear cells, increase in polymorphonuclears, transient decrease in leukocyte count. Leukemic blood picture subsequently returned.

Fraenkel (56): Two cases of lymphatic leukemia in which sepsis developed. There was very marked decrease in the leukocytes and shrinking of the lymphatic tumors, followed by death.

Richter (206) concluded that the leukocytosis increased the number of mature polymorphonuclears which are insufficiently produced in leukemia, and that the convalescence and apparent cure in his own case was due to the regeneration of the blood and increase in the nucleated erythrocytes. As to the practical considerations of this phenomenon, Richter stated that if the hyper-leukocytosis supplies the blood with mature and healthy cells, and later keeps stimulating the blood-forming organs, we should artificially administer those toxins which are known to exert these effects.

Richter believed that Heuck was the first to attempt such a procedure when he injected *tuberculin* in a leukemic woman, causing a drop in the white blood cells. Sometime prior to the publication of his paper in 1896, Richter injected "Zimmsante" intravenously in a case of lymphatic leukemia. There was a sudden sharp rise in the polymorphonuclears (49—86 %), while the mononuclears decreased to 14 %. Then there was a rapid decrease in the leukocytes, followed finally by a return to the leukemic status 24 hours after injection. Four days later the leukocytes were reduced to 25 % of their former number. Thereafter there was a slow return to the former status. The blood changes were accompanied by a decrease in the size of the spleen. Richter thought it striking that the leukocytes had increased at first, and that this had soon been compensated. He believed that the temporary hyper-leukocytosis improved the blood for some time through production of the polymorphonuclear cells.

He then cited a third case in which this idea was tried: Jacobi's, in which a leukemic patient was injected with a leukocytosis-promoting material (he did not state what was given), followed by temporary decrease in the number of leukocytes.

Richter himself had a similar result with an injection of spermine (a testicular extract) in another leukemic patient, the white blood count falling from 224,000 to 106,000. He concluded that these few and rather uncertain observations called for further research on this problem (206).

Weil (255) believed that Muller was the first to suggest the use of *bacterial toxins* as a therapeutic measure in leukemia, and he thought that up to 1900 no one had yet attempted to do so. Weil believed that such attempts were justified, first because they imitated a natural process, and also because the disease is fatal and incurable with any other method. He suggested that the administration of arsenic might also be employed, in the form of sodium cacodylate, which acted so well in leukemic patients in improving the red blood count.

Weil also noted that leukemia is frequently complicated by various infections, especially *streptococcus, bacillus coli* and *pneumococcus*; that infection is most frequently the cause of death in leukemic patients; and that sometimes these infections are localized, but more often tend to generalization and septicemia.

He analyzed the modifications in the leukocyte formula produced by infections, noting that these effects are temporary. After a time, the leukemic patient no longer responds to the effects of the infection and the course of the disease proceeds. The

modifications are (a) in myelogenous leukemia there is a diminution of the leukocytosis, with almost complete disappearance of the granular mononuclears; (b) in lymphatic leukemia the infections cause a decrease, sometimes enormous, of the total leukocytes; (c) in acute leukemia, the leukocytes diminish considerably, almost completely; (d) as to the leukemic tumors, all infections cause their regression, more or less marked. Certain infections have a more marked effect in leukemia, streptococcus being apparently the most active.

Marischler (1896), Thorsch (237) and Neutra (188) reviewed the early cases and Dock (38) made the most intensive study of the changes which occur in leukemia associated with intercurrent disease of anyone who had investigated this phenomenon. He stated that cases of this kind were rapidly multiplying in the literature and that a study of these and others might prove useful.

After describing in detail his own most important case (see table, case 2), Dock (38) discussed the implications. His patient was a woman with mixed cell leukemia and a greatly enlarged spleen, in which two weeks after an attack of what was probably *influenza*, the leukocytes were reduced from 367,000 to 7,500; falling to 4,775 in another two weeks, with reduction but not disappearance of the abnormal white and red blood cells. The spleen became much smaller and remained small for many months.

Dock stated: "Such a change, more marked than one usually sees in leukemia under treatment, forces one to try to learn something from it, not only as regards pathology, but, even more imperatively, something of therapeutic value. The most important objective symptom, the excess of leukocytes, disappears. It would seem that by examining such cases one might discover something regarding the production of leukocytes and their appearance in the circulation, as well as their ultimate destruction. Also this might show something of the life of the red blood corpuscles, and of other details of the pathology of leukemia.

"It would seem that the process might be imitated and a symptomatic if not a causal treatment be discovered. Medical literature contains a number of such cases, though not so many as one might expect remembering the vulnerability of the leukemic to infection" (38).

The combination of *tuberculosis* and leukemia was noted very early—Virchow described it in 1849. Over thirty cases were reported up to 1904. Dock concluded after carefully analyzing these data: "From the available material it appears that chronic tuberculosis does not distinctly influence the course of leukemia or influence the leukocyte formula. Acute miliary tuberculosis, on the other hand, is followed by or associated with the reduction of the leukocytes in the majority of cases." The exceptional cases Dock felt might be due to the fact that death occurred before the change had had time to take place, or because the infection was minimal, or it may be as Roth suggested that the body becomes accustomed to the infections and the leukocytes are not affected as in the more acute cases. (Note: It is significant that these same observations hold for the effect of tuberculosis on malignant

tumors: chronic or mild, attenuated tuberculosis had little or no effect on the course of the malignancy, while acute miliary tuberculosis did cause a few regressions, or slowed the progress of the malignancy. For a recent case see Heinle and Weir (89). However, tuberculosis did not appear to be nearly as effective as streptococcal infections in causing complete regression and permanent freedom from recurrence in patients with neoplasms.)

Dock found 23 reported cases of *infections other than tuberculosis* which occurred concurrently with leukemia. There was marked decrease of leukocytes to normal or nearly normal in eleven of these: Eisenlohr (43), a typhoid-like disease; Kraus (127), erysipelas, streptococcus and diplococcus infection; Frohlich (59), pneumonia; Fraenkel (56), two cases, one staphylococcus, one colon bacillus; Oette (190), pneumonia; Kormoczi (125), sepsis; Dock (38), influenza; E. Muller (177), streptococcus, staphylococcus and colon bacillus; Cabot (24), sepsis. There was relatively slight decrease in leukocytes in nine cases: Pal (192), afebrile typhoid; Richter (206), erysipelas after puncture of the tympanic membrane; H. F. Muller (178, 179), two cases of sepsis; Weil (255), streptococcus; Thorsch (237), pneumonia in a case of chronic lymphatic leukemia; G. Heuck (98), empyema; Grawitz (82), pneumonia. There was no change in the leukocyte formula or a rise in three cases: Muller (178, 179); Pettit and Emile-Weil (198), a chronic lymphatic leukemia, in which bronchitis developed causing death in six days: wbc rose from 202,238 to 398,866; Da Costa (1904, cited by Dock 38), splenomedullary, in which 10 days after onset of peritonitis the wbc rose from 245,000 to 400,000. In all three of these cases, the rise of leukocytes was discovered early in the complicating infection, the patient dying soon after. Dock observed: "It is possible that a fall might have occurred after the rise had the cases ended less abruptly. The earliest period after complication has rarely been observed, and should be thoroughly studied in the future" (38).

He concluded from the foregoing observations that in the great majority of cases concurrent infections cause a decrease of the leukocytes in various types of leukemia. The fall may be so slight as to leave the gross picture unchanged, but in half the cases the white blood corpuscles fall to normal or below. It is interesting to note the extreme leukopenia that occurred in some cases: 600 wbc in Wende's (258); 471 in Cabot's (24); 2,000 in Kormoczi's (125).

Besides the decrease in leukocytes, the organs, enlarged as a result of leukemia, become smaller. In some cases this occurred later than the fall of leukocytes: Quincke (203), miliary tuberculosis being the complicating infection. In other cases it occurs earlier and sometimes simultaneously. In still another case, the organs became smaller without diminution of leukocytes: H. F. Muller (178, 179); Pettit and Emile-Weil (198): the case of chronic lymphatic leukemia with complicating bronchitis. The diminution was sometimes very rapid. Quincke estimated the change in the volume of the spleen to be 100 grams a day, a rate which Dock believed must have been exceeded in his own case.

He stated that the changes in the leukocyte formula are not uniform though

there is a disposition for the leukemic character to disappear more or less completely under the influence of infections, and for the polymorphonuclears to increase absolutely as well as relatively. In general, the changes occur soon after the infection, more promptly in acute than in chronic infections.

Dock then reviewed the literature on the use of various drugs, such as iron, arsenic and its salts, phosphorus, quinine, oxygen, etc., stating that the drugs which some had found most valuable had failed entirely in the hands of others. The literature is largely available in the study of Behsemeyer, 1894, cited by Dock (38).

A number of observations have been published on the action of *organic extracts and bacterial products* on the leukemic subject. Dock described the effects of tuberculin injections, as given by Heuck in a leukemic patient who had slight signs in one apex, but no bacilli in the sputum and no reaction to 5 milligrams of tuberculin. He injected 19 doses of from 10 to 20 mg, causing reactions "like those of phthisis". From the 12th injection (60 mg), there was a fall in the leukocytes each time, quickly returning though not quite to the previous number. There was general improvement, with diminution of the size of the glands.

Pal (192) also used tuberculin on a leukemic patient, noting decrease in leukocytes after six hours, followed next day by a rise, the temperature and subjective symptoms being worse. It is significant to note that Pal purposely avoided marked reactions, "in order to avoid severe effects on nutrition".

Beitzke (5) used tuberculin in six leukemic patients in Quincke's clinic. The results were very uncertain, the injections not being continued long enough to permit conclusions to be drawn, and other treatments being carried out at the same time. Two patients showing the most distinct improvement were also taking arsenic.

Pollitzer (20) gave tuberculin in a case of medullary leukemia in doses of 2 to 200 mg without reduction of leukocytes, but with increase in the size of the spleen and more marked cachexia. In a case of lymphatic leukemia, tuberculin was given for two weeks in doses of 2 to 64 mg, with a gradual but slight rise of leukocytes without change in the formula. Nuclein was also administered in both these cases.

Weitz (256) used tuberculin on several cases of leukemia. He reported the action appeared favorable until the patient's organism became accustomed to the toxins contained in the tuberculin.

(It would appear from the available evidence on both cancer and leukemia patients who were treated by injections of tuberculin, that this form of bacterial product was not as effective as the mixed toxins of erysipelas and bacillus prodigiosus ("Coley toxins") in producing regression or apparent cure in neoplastic diseases.)

Dock also cited Jacobi's case in which a splenic extract was given to a leukemia patient subcutaneously, at intervals of two to four days. These injections cause sweating, anxiety, dyspnea, etc., attributed to congestion of the lung capillaries. There was a slight rise in leukocytes followed by a fall to half the number prior to beginning these injections, as well as increased excretion of nitrogen in the urine.

In conclusion, Dock stated that these few experiments indicated the need for

further study. The blood must be examined at short intervals after the treatment is begun, differential counts must be made. Careful observation of the entire body, including subjective symptoms and metabolic changes, are also desirable. He added: "Full and satisfactory explanation of the changes observed in leukemia under the influences of other diseases does not seem possible at present. We are still too much in the dark regarding the cause of leukemia, the nature of the changes in the tissues, and the mechanisms of the blood changes and we are only beginning to know something of the effects of infections and intoxication on the blood forming organs and the circulating blood."

"An early and natural explanation was that disease associated with leukopenia or without leukocytosis in ordinary cases caused in leukemia a decrease of leukocytes. This might apply to miliary tuberculosis or typhoid fever, such as Eisenlohr's case was supposed to be. But further reports not only opposed this view, but led to the oppcsite one, viz., *that disease ordinarily causing leukocytosis has an antagonistic effect in leukemia* . . . The leukocytolytic theory of Fraenkel is also attractive. It seems born out by the author's observations on degenerated leukocytes in h s own cases, and the increased excretion of uric acid. It seems analagous to the rapi¹d disappearance of certain tumors, some of which (sarcoma) closely resemble leukemia growths, under the action of poisons like arsenic or those of certain infections, such as erysipelas . . . Quincke's objections, that no evidence of transfer of leukocytes is present, might be explained by a breaking down of the cells . . ."

"It seems to me, the process in most cases is complex. Breakdown and consumption must occur in cases with severe cytolytic poisons, and in some must preponderate. In others chemotactic processes will be most important, and innumerable variations in the clinical course and the blood picture will probably depend partly on the kind, extent and intensity of the intoxication, partly on the histological peculiarities of the new growths, and the capacity of their cells to be poured into the circulation. Thus in acute lymphatic leukemia, the changes will not be the same as in chronic myeloid alteration of all the blood-forming organs."

"Finally, the question of therapeutic value: it is easy to understand how many have looked upon the changes cited above as evidences of healing. The most striking sign of leukemia, the excess of leukocytes, disappears, and sometimes the spleen and lymph glands return to normal size. Yet that the change is not wholly favorable, appears from the fact that no case has really recovered. Most cases died while under the influence of the process that was thought to have healed them, and although some seem to have had their lives prolonged none have lived longer than many leukemics without such complications" (38).

"Weil has suggested that the action of the complicating infections is 'too brutal' and this may be so, although the cases hitherto observed show considerable variations in severity. But considering the hopelessness of the ordinary treatments of leukemia it seems that carefully planned experiments with either bacterial products or organ extracts might show a safer and more permanent result" (38).

Forkner (54) discussed the effects of *malaria* on the incidence of leukemia or on its course. He cited a number of authors who thought that attacks of malaria predispose individuals to leukemia: Mosler (1872) apparently was the first to emphasize this point of view. Gowers (1879) reviewed 150 cases of leukemia and found a history of malaria in 30. He stated that leukemia bore a closer relation to malaria than to any other disease, and thought leukemia might occur as an effect of malaria, which had not produced intermittent fever. Aubertin, who since 1906 has believed malaria to be a predisposing cause of myelogenous leukemia, reaffirmed that viewpoint (1932) and has supported his contention by reports of two additional cases. Leesch (1932) noted the appearance of chronic lymphogenous leukemia after the treatment of syphilis by means of inoculation with malaria. Luisada (1933) considered malaria as a possible etiological agent in a case of chronic lymphogenous leukemia. Reynolds (1933) and Stancanelli (1933) suggest that their cases of acute lymphogenous leukemia might have had their origin in frequent attacks of malaria. Blanc (1933) shares the view of Aubertin and is convinced that the association of leukemia and malaria is more than a coincidence. He suggests that a plausible theory of the mechanism of the production is that the sexual forms of the parasite remain for long periods in the bone marrow and spleen, where they produce mild prolonged stimulation of the hematopoietic tissue, finally terminating in chronic leukemia. Many other workers have failed to note any relationship between leukemia and malaria (54).

Several physicians have reported cases of leukemia in which malaria developed accidentally. Nammach (1895) and Villa (1928) observed no improvement in patients with chronic leukemia who developed malaria. Macfie (147) reported two cases personally observed that were benefited. In the first, a lymphatic leukemia, the leukocytes were reduced from 286,000 to 59,000 after the malaria developed. The patient then disappeared so the final course is unknown. In the other, a myelogenous leukemia, the leukocytes fell from 326,000 to 62,900. The reduction was not permanent and was rapidly effaced by treatment with quinine.

Since malaria was a disease that could be inoculated and eliminated promptly and completely by quinine, it is not surprising that it was the first infection to be induced therapeutically in cases of leukemia.

Schupfer (220) was the first to do so. He inoculated a patient suffering from myelogenous leukemia with quartan malaria. He observed a reduction in the leukocytes from 82,000 to 13,600. No striking change occurred in the differential count. After treatment of the malaria with quinine the leukocyte count rose rapidly. Rudolph (213), Rosenow (209—210) and Gamble (73) stated that Lucherini (1927), Paschkis (1932), Luca (1933) and others have confirmed Schupfer's observations. Klauder noted striking improvement in four out of five patients with mycosis fungoides treated by means of inoculation with malaria. Moretti observed no apparent benefit from infection of a leukemia patient with the spirochetes of relapsing fever (213).

Forkner (54) also noted that Izar (131) had claimed to have cured a case of chronic myelogenous leukemia by means of *fever therapy*. He used injections of a commercial sulphur preparation (see table, case 30).

Izar treated a number of leukemia patients in this way, stating that the administration of sulphur injections produced a more or less specific febrile reaction in all the cases. He believed the optimum febrile reactions should be between 2° and 3°C.

Izar found that a dose of 5 cc would consistently produce a fever of 39°C in the "cured" case, while in another patient it would produce only 38°C. To determine the sensitivity of each patient a dose of 5 cc was given. If necessary this amount was increased or decreased to produce the desired reaction. He suggested that to determine the optimum dose one should begin the treatment with injections on alternate days given at the same hour, preferably in the evening, using the same dose of sulphur preparation, given deeply in the gluteal muscles. The rise in temperature was not preceded by any other reaction phenomenon. The patients only felt a sense of general prostration with pains in the muscles and joints "which one observes with said fevers from the beginning". Rarely do they have cephalagia, never intense. The rise of fever is not rapid, the peak being around 10 or 12 hours after injection. Following a period of four to six hours at which the temperature remains elevated, it then falls gradually, reaching normal about 24 hours after injection. By giving a day of rest between injections one has a 24 hour period without fever. The local phenomena are always minimal, if one is careful to use alternate buttocks. Izar urged aseptic precautions to prevent suppuration. The pulse and respiration follows the rising temperature. The digestion and psyche are unaffected. Izar believed that the effects of this treatment on leukemia may be determined by studying the following factors:

1. Condition of patient: On this the influence of sulphur therapy is clear and evident. In all the patients the general condition, which is very precarious when they enter the clinic, improves from the first injection, "accompanied by a marked subjective sense of well-being, a real sense of euphoria, which rarely one can observe in this form". Also in the more resistant patients, notwithstanding the long persistence of immature forms of leukocytes in the circulation, symptomatic improvement apparently occurs.

2. The reaction of the hematopoietic system, the spleen and the lymphatic glands: "One can affirm that the splenomegaly decreased rapidly after the first injection of sulphur while at the same time the hypertrophy of the peripheral lymphatic system reduced until it has practically disappeared. To assume that in all cases the spleen will reduce to its original size is hazardous if not impossible."

3. White Blood Cells: The leukocytes diminish rapidly beginning right after the first injection of sulphur, and the immature forms disappear in a progressive and persistent way. The diminution and disappearance of immature forms is slow

in appearing and comes in stages, from the younger elements to those less immature. See Izar (131), p. 859 for details.

The first injection produces a massive reaction analagous to the response to x-rays. The second injection consolidates this effect with a gradual disappearance of the immature elements which one does not see following other forms of treatment. There is a distinct and differentiated non-specific pyrogenic effect from the action of the sulphur element in particular. The initial response to a common sulphur preparation was a rapid and marked decrease in the number of leukocytes and of immature forms, but the disease did not appear to be under complete control until a more potent sulphur preparation was tried.

Although the present study is concerned with the effects of concurrent infections or their toxins on leukemia it seemed of interest to consider the possible benefit of fever induced by other means in such cases. The rarity of Izar's observations suggests the need for further studies.

Jaffe (113) discussed the *inflammatory defense reactions* in leukemia, noting that few histologic studies on inflammation in leukemia existed and the recorded observations are contradictory. He concluded:

"Provided some myeloid tissue capable of maturation is left, the leukemic organism reacts to an infection like a normal one . . . The literature contains many observations dealing with the return of normal blood findings in leukemic patients during or after an intercurrent infection: Allacia, 1902; Kormoczi (125); Funk, prior to 1925; Naegeli (102); Dock (38); and others . . . The restoration of a normal hematopoiesis in leukemia under the influence of an infection cannot be compared with the disappearance of an epithelioma of the skin over which erysipelas is spreading, since one is dealing not merely with a regression of the leukemic tissue but with the resumption of an exceedingly intricate function by the diseased organ." If granulopoiesis is completely exhausted there is no defense reaction to an infection. As far as the inflammatory reactions are concerned there is no difference between the acute and chronic leukemias.

Jaffe gave the histologic pictures of the inflammatory defense reactions in 10 cases of leukemia. He showed that the type of response depends on the presence of myeloid tissue able to produce mature granulocytes. In the presence of such tissue, the leukemic cells react to an infection like a normal person, while in their absence the leukemic cells are not able to compensate and the alternative changes predominate as they do in agranulocythemia and aplastic anemia.

The third patient in Jaffe's series, who had subacute aleukemic lymphadenosis changing later into the leukemic form, developed a complicating infection which was followed by a streptococcal septicemia. "Under the influence of the septicemia the white count dropped within a few days from 53,000 to 850 and save for the severe anemia the blood picture finally resembled an agranulocythemia. About the necrotic lesions in the mouth there was not a single granulocyte and the lymphatic

elements were unable to compensate for the lack of leukocytic response. Nowhere in the body were there any myelocytes . . . In the lymph nodes and in the spleen the leukemic cells revealed very severe regressive changes, which caused a peculiar loosening of these organs. In the bone marrow and in the liver the disintegration of cells was much less marked . . ."

"One of the most interesting observations is the combination of acute myeloblastic leukemia with metastases of a melanoblastoma of the eye to the liver and a syphilitic granuloma of the lung. The combination of leukemia and malignant tumor is very rare. Hirschfeld (101) cited Gluckmann and Luder; Marischler, 1896. It has been said that when a malignant tumor develops in a leukemic patient, the leukemic symptoms may regress." (Zadek, cited by Hirschfeld 101.) In Jaffe's case there was no interference between leukemia and tumor, and in the liver the two types of cells were found growing side by side.

Jaffe noted in the course of this study that *"the leukemic organism does not seem to have lost the ability to produce normal blood cells (113) and this ability can be awakened by bacterial toxins"*.

Cantieri (26) reported a case of lymphatic leukemia in which a remission lasting two months occurred following the development of a *suppurative process* localized to the patient's thighs. He emphasized that the suppurative process had been the cause of the remission, and supported this view by the findings of other investigators. He cited two recent observations of French authors in which the long duration of the remission which had followed suppurative manifestations, had been attributed to the beneficial effects of blood transfusions. On the basis of these various cases Cantieri suggested that in cases of leukemia one might consider the use of fixation abscesses, as a means of inducing remissions.

In 1950 Shear noted that among several hundred children with untreated leukemia in the Children's Hospital in Boston, brief remissions were observed in 9.5 % of these cases. In 75 % of these spontaneous remissions, the remission was preceded by an episode of acute infection. Shear went on to say: "Remarkable progress is being observed in the control of infectious disease. Concurrently . . . there is an increase in the incidence of malignant diseases even when figures are corrected for improved methods of diagnosis and for age distribution. Are pathogenic and non-pathogenic micro-organisms one of Nature's controls of microscopic foci of malignant tissue, and, in making progress in the control of infectious diseases, are we removing one of Nature's controls of cancer?" (223).

Southam, et al (228) in a study of the natural history of leukemia, discussed the occurrence of remissions. It was found that seven of the 16 cases they reported in detail as having complete or partial remissions, had had concurrent infection or fever immediately prior to the remission. (See Table for these cases.)

In February 1952 Cappell, Professor of Pathology at Western Infirmary, Glasgow, Scotland, observed a case of acute leukemia in which all the leukemic changes disappeared from the blood and bone marrow following a *staphylococcal pneumonia*,

through which the patient was kept alive by penicillin. The patient subsequently developed multiple chloromatous tumors in the breasts and paravertebrally and died as a result of pressure on the cord (2 a).

Bierman and his associates (9) studied the effects of concurrent infections on leukemia. Their interest was aroused by a striking example of these effects on a 14-year old boy with lymphatic leukemia who developed a severe *hemolytic streptococcal septicemia*, followed by a complete remission lasting two months.

In reviewing the more recent literature they noted that until a few years ago, "spontaneous" remission of leukemia in children was considered a rare event. Dreyfus (39) was able to collect 21 cases in the literature, and Birge, Jenks and Luhby (10) found 26 remissions among 270 patients with "blast cell" leukemia. These were preceded by a marked leukopenia and hypoplasia of the bone marrow. In 11 of the 12 "complete" remissions, and in 10 of the 14 partial remissions, severe infection preceded the hypoplastic stage.

Bierman's group observed four children with leukemia who developed acute generalized hemolytic *staphylococcus aureus* infections. In two others staphylococcus infections were present in addition to varicella and the inoculation of feline agranulocytosis virus. They concluded that hemolytic staphylococcus appears to have been the dominant organism involved although in three children streptococcus viridans and staphylococcus albus were also recovered.

Four other children developed *varicella* with their disease. One of the children died within three days of the eruption. No hematological studies were performed during this period and the case was not reported. The other three cases were reported in detail (see Table). On the basis of the effects observed in case 5 an attempt was made to infect six other leukemic children with varicella. Four children failed to develop evidence of varicella and the remaining two died during the incubation period. All, however, had received transfusions of adult blood for their anemia, so that Bierman felt that passive immunity against varicella may have been responsible for the inability to transmit the disease.

Because of the specific leukocyte changes produced by *feline panleukopenia*, a viral disease of cats associated with profound leukopenia, Bierman's group studied the possible effect this disease might have on childhood leukemia. Six children with lymphatic leukemia were inoculated with feline spleen suspensions containing this virus. One child died within 12 hours of an intracranial hemorrhage, and another within 12 days of leukemia without any effects that could be attributed to the procedure. Data on the remaining four children were given in detail in their report.

In discussing the clinical effects produced by concurrent infections they outlined the sequence as follows: "A child with lymphatic leukemia, with a high or a low leukocyte cell count, and with or without a marked granulopenia, develops an infection that is followed by fever, marked drop in the peripheral leukocyte count, and with or without a marked granulopenia, and occasionally a hypoplastic phase

in the bone marrow. If the patient survives this phase, the hemogram returns to normal and a temporary clinical remission may occur.

This course of events was seen with hemolytic staphylococcus aureus, and with varicella and probably following infections by other bacterial or viral entities. No common denominator regarding the organism, therefore was apparent. All patients had a febrile episode during the height of the infection. Fever per se, however, is difficult to accept as the explanation of the effects, since many children with leukemia develop febrile episodes and long continued high fever without manifesting the course of events observed with acute infections . . ."

"The observation that a frankly leukemic picture can be transformed in a few days to resemble the normal clinical and hematological appearance is a strong indication that some leukemias are reversible. The rapidity and degree of this return toward the normal suggest that physiological imbalance of the hematological system may be a major component of the disease. If the balance between the normal and abnormal is so precarious in this group of diseases that it can be upset rapidly and to a great degree by a mild virus injection such as varicella, the outlook for similar and perhaps more prolonged alterations appears promising. That this balance is not solely confined to the leukocytic elements is supported by the associated return toward normal levels and behavior of the erythrocytes and platelets. The definite and objective effects observed are of great research interest and indicate the importance of more extensive, more controlled observations, as well as of specifically designed clinical experiments on the effects of induced infections in childhood leukemia" (9).

Huth (108, 109, 110) has extensively reviewed the literature on so-called "spontaneous" regressions or remissions in neoplastic diseases, noting that in most of the reported cases infection or fever occurred, or toxin therapy was used. In addition to the cases cited by earlier authors he mentioned Moeschlin's (166) observation, in which remission followed staphylococcal abscess formation at sites of injected medication, also Hopfengartner's case as the most recent example of the effects of tuberculosis on leukemia (103). Huth also mentioned Taylor's (236) observation of the beneficial effects of infectious mononucleosis, both spontaneous and induced, on several leukemia patients. Huth's conclusions as to the effect of concurrent infections on leukemia are basically in agreement with those of Bierman's group.

Huth believed the rarity of remissions in leukemia is apparently due to the fact that the body must still be able to limit the infection. This defensive power is lost in the course of leukemia. The cases in which remissions occurred usually concerned first remissions in the early stages of the disease. The more advanced the leukemia the less it can be influenced. Infections developing in the final stages may have only a deleterious effect, without benefit to the leukemic process.

Huth (188 a) is now administering bacterial products to children with leukemia. He believes that such therapy should be begun early in the course of the disease,

prior to radiation or other therapeutic agents, and that it should be continued during remissions.

The following table includes representative cases which indicate the changes which may occur in patients with leukemia following concurrent infection, fever, or injections of bacterial products. Some of the earlier cases may be questioned because of the lack of bone marrow studies to confirm the diagnosis. A study of all the recorded cases suggests that patients who developed tuberculosis or malaria did not usually respond as dramatically as did those with pyogenic infections.

CONCLUSIONS:

Many factors appear to influence the incidence and progress of leukemia. Certain drugs or chemicals, such as some of the sulfonamides, chloromycetin, cortisone, butazolidin and benzol; estrogenic hormones; and various forms of irradiation may be leukemogenic and some of them also appear to decrease natural resistance to cancer as well as leukemia.

Acute concurrent bacterial infections or their toxins, or other substances that stimulate acute inflammatory reactions and the reticulo-endothelial system, appear to increase natural resistance to neoplastic diseases. When acute infections develop concurrently with cancer or leukemia they may cause complete or partial regression or remission. In cancer patients such complete regressions have been permanent in 62 cases traced from 5 to 44 years after onset. In leukemia they have thus far been only temporary. They have been observed most often after staphylococcal or streptococcal infections, rather than malaria or tuberculosis, or viral infections.

The incidence of cancer and leukemia is considerably lower at present among peoples such as the American Indian, who still have a higher incidence of infections and infectious diseases than the white race in the United States.

Since it is now possible to control induced infections with antibiotics, further studies on the therapeutic effect of such concurrent infections in leukemia may now be instituted as soon as diagnosis is proven. Fixation abscesses may be a good way to utilize this effect, as suggested by Cantieri. The effects of such infections may be then compared with bacterial products such as the mixed toxins of Streptococcus hemolyticus and Serratia marcescens, known originally as Bacillus prodigiosus (Coley Toxins).

The optimum technic of administration of bacterial products for leukemia patients must be carefully evaluated as to site, dosage, frequency and duration of injections. Since mild, low-grade infections seldom exerted any marked benefit on leukemia or cancer, treatment should be given aggressively enough to imitate more severe infections, i.e., inducing sharp febrile reactions of 102—104°F, with chills, rather than merely malaise and one or two degrees of fever. However, one must guard against blocking the reticulo-endothelial system by too large doses. In leukemia

patients smaller doses of bacterial products produce the desired reactions than in other types of neoplastic disease.

A study of the effect of Coley Toxins in over 1,200 patients with malignant disease of various types indicates that many failures may have been due to inadequate technic as regards site, dosage, frequency and duration of the injections, others to the use of weak, variable toxin preparations, and many others to delaying the treatment until heavy radiation had been used, or the patients were in the terminal stage. Since radiation depletes lymphoid tissue and depresses the reticulo-endothelial system, each of which may play a significant role in natural resistance to neoplasia, one must begin toxin therapy prior to irradiation and one must avoid using large doses of x-ray in various forms of neoplasia including leukemia.

Now that these factors are beginning to be recognized, greater progress may result in the treatment of leukemia and other neoplastic diseases by means of toxin therapy.

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CASES IN LEUKEMIA

in which a cute infection developed

CASES OF LEUKEMIA

in which acute infection developed

Cases of leukemia in which acute infection developed, fever was induced or bacterial products were injected.

Author References	Date of Onset	Age Sex	Type of Leukemia	Type of Treatment Prior to Infection	Type of Infection Fever, Injection	Effect of Infection Fever, Injections	Period of Survival
1. Richter 38, 82, 136, 206	1885	female 21	advanced myelogenous	apparently none	facial erysipelas	spleen diminished in 5 days, wbc fell from 320,000 to 56,000; normal differential; general condition improved; symptomatic cure.	death 6 mos. after infection, cause not given
2. Dock 38	1897	female 42	mixed cell myelogenous	Fowler's solution	influenza tonsillitis coryza	dramatic drop in wbc: 376,070 to 4,775 in 3 weeks; reduction but not complete disappearance, abnormal red and white cells; spleen much smaller, liver smaller; both normal in 9 weeks; gained 8 lbs.; 2 months after infection wbc 40,000; year later 461,000; liver and spleen normal many months.	death 18 mos. after infection
3. Galloway 72	1910	male 47	splenomedullary	arsenic	nasal catarrh "severe cold" facial erysipelas	remarkable improvement evident immediately after erysipelas: spleen receded, wbc fell from 284,000 to 36,000 during infection; rbc rose from 2,280,000 to 3,440,000; hemoglobin also increased; general condition markedly improved.	alive when case was published
4. Veyssi 247, 261	1934	female adult Bedouin	advanced myelogenous; generalized emaciation; anemia	14 live cauteries on abdomen by Bedouin marabout	very marked suppuration of all 14 cauteries, high fever, lasting eight weeks	patient recovered; excellent general condition; wbc fell from 380,000 to 80,000; rbc rose from 3,200,000 to 4,100,000; differential improved. Remission temporary.	death 18 mos.
5. Marchal 154	1/41	female 57	acute cryptogenic following prolonged use of pyramidon, sulfonamide	injections "Campolan"; pentonucleotide; vitamin PP; liver extract	perianal abscess; another at site injections medication; abundant thick pus; buccal phlegmon following tooth extraction	blood improved after each abscess developed; after second one amelioration lasted 5 months; progress of the acute leukemia considered to be remarkably slow.	death 21 mos.

6. Southam 228	8/1/35	male 14	acute lymphatic	total body irradiation (25 r); caused leukopenia; blood transfusions	severe necrotic buccal ulcerations; acute necrotizing arteritis; terminal bronchial pneumonia	remarkable subjective improvement; remission lasted only 2 weeks; further oral ulcerations; post-mortem revealed only minimal evidence leukemia, diagnostic only in bone marrow; spleen empty of lymphocytes, reduced to connective tissue skeleton.	death 2 ½ mos.
7. Southam 228	2/42	male 9	acute (myeloblastic?)	injections liver, pentonucleotide; x-ray therapy; no benefit noted	fever 100-104°F, submaxillary abscess; drained; fever continued during daily transfusions	during febrile period wbc fell to 10,000; spleen regressed partially; symptomatic improvement; no improvement in differential; 4 weeks later, without further therapy differential improved, patient felt well, gained weight. Further course relentlessly down-hill.	death 11 mos.
8. Southam 228	2/44	male 20 mos.	acute lymphatic	transfusions, sulfadiazine for fever	fever to 104°F	marked clinical improvement; nodes, liver, spleen receded partially; wbc fell from 47,850 with 90% blasts to 6,600 with 3% blasts; partial remission lasted 2 weeks.	death about 4 mos.
9. Southam 228	1/17/47	female 4	acute lymphatic	transfusions	lobar pneumonia; terminal pneumonia	general condition improved; wbc fell from 100,000 to normal; with 30% polymorphs, 70% blasts; partial temporary remission.	death over 3 mos.
10. Southam 228	12/46	male 3	acute lymphatic	SKI 136 transfusions	spiking fever: malaria (transmitted accidentally by transfusion)	marked regression liver, spleen, nodes, and normal cellularity followed malaria; terminal high fever; at autopsy no evidence leukemia in organs or blood; marrow markedly hypoplastic.	death 10 mos.
11. Southam 228	4/47	female 4	acute myeloid, following sulfonamide therapy	many transfusions during throat infection	throat infection after tonsils and adenoids removed	remission after throat infection; appeared perfectly well; hemoglobin rose; remission lasted about 2 mos., condition then failed, did not respond to infusion toluidine blue or further transfusions.	death about 5 mos.

Author References	Date of Onset	Age Sex	Type of Leukemia	Type of Treatment Prior to Infection	Type of Infection Fever, Injection	Effect of Infection Fever, Injections	Period of Survival
12. Southam 228	4/1/48	male 10	acute monoblastic? intense dyspnea; cyanosis	None	throat infection; fever 102°F or more, persisted despite intensive penicillin; pharyngeal edema, tracheotomy	following persistent febrile episode peripheral blood showed progresrive change toward normal; complete subjective remission lasting 8 weeks.	death about 5 mos.
13. Cantieri 26	?	female 14	lymphatic condition grave	several transfusions	suppurative process on thighs	complete hematological remission lasting 2 mos.; rapidly fatal termination in spite of penicillin. (Cantieri suggested inducing fixation abscesses on basis of this and similar cases.)	death 10—12 mos.
14. Bierman 9	1/40	female 6	acute lymphatic	transfusions, pentonucleotide; yellow bone marrow extract; vitamin K and C (no marked benefit noted)	varicella; also localized infections at sites cut-down venoclysis; cellulitis, septic fever 10 days; final frank septicemia (staph. and strep.)	clinical and hematological remission lasting about 5 weeks; then reversal of blood picture and clinical deterioration; lived 4 mos. after onset of infections.	death 6 mos.
15. Bierman 9	2/51	male 4	acute lymphatic	saccharated iron i.v. no effect	fever 38.6°C. with varicella (severe hemorrhagic eruption)	rapid dramatic remission: wbc fell from 300,000 to 7,500 in 4 days; liver, spleen barely palpable; given corticotropin to depress immune response; almost complete remission 1 month; (infection and return to normal peripheral blood occurred without preceding agranulocytosis).	death 6 mos.
16. Bierman 9	11/14/48	male 2	lymphatic	aminopterin repeated transfusions	severe staph. aureus infection left calf; fever 39.7°—41C; thrombophlebitis; lung abscess; osteomyelitis hip.	hematological improvement lasted 2 weeks, no clinical remission.	death 3 mos.

17. Bierman 9	4/49	female 7	lymphatic	transfusions	spleen suspension feline panleukopenia virus inoculated; fever to 39.8°C; abscess left submaxillary	hematological changes followed abscess formation; minor rise in granulocytes, maintenance of hg; clinical improvement; (no evidence panleukopenia was transmitted).	death 8 mos.
18. Bierman 9	6/49	male 14	fulminant lymphatic, with granulopenia progressive anemia, critically ill	progressive anemia despite transfusions prior to infection; 4 more transfusions during infection: hg then rose to 8.9; 3 more and it rose to 14 gm	spiking fever; pneumonia (hemolytic staph. aureus); also bulla left ear; penicillin; another acute infection, same organism.	during height of infection dramatic fall in peripheral wbc (55,000 to 120 per cu mm); bone marrow became aplastic; liver, spleen rapidly decreased, no longer palpable in 3 days; hg increased; marked clinical improvement 48 hours after wbc had fallen; gradually stronger, ambulatory; clinical and hematological remission lasted 6 weeks; another frank leukemic period for 1 month; after 2nd infection another dramatic fall in leukemic lymphocytes, but no change in leukemic bone marrow. Short course ACTH, death soon after.	death 7 mos.
19. Bierman 9	4/51	male 4	acute lymphatic	none	submandibular abscesses, fever to 39.5°C, incised, drained purulent material; embolic abscesses, nose, right leg (non-hemolytic staph. albus, aureus, diphtheroids); spiking fever 40°C; repeated infections next 4 mos.	marked clinical improvement, improved blood picture; 5 weeks later total leukemic syndrome returned; during one infection extremely enlarged liver decreased rapidly toward normal for 2 weeks.	death 12 mos.

Author References	Date of Onset	Age Sex	Type of Leukemia	Type of Treatment Prior to Infection	Type of Infection Fever, Injection	Effect of Infection Fever, Injections	Period of Survival
20. Bierman 9	12/51	female 22 mos.	fulminant lymphatic (moribund)	transfusion (very anemic)	infected hemorrhagic skin lesions, chest, groin, feet; deep abscess over scapula, bilateral otitis media; (hemolytic staph. aureus, few colonies strep. viridans)	At height of infection aplastic blood picture reversed sharply toward normal, with normal differential; platelets, rbc & hg also rose to normal; neurological symptoms disappeared; spectacular rapid recovery; clinically well except for bilateral perforation both ear drums, persistent purulent drainage.	death 9 mos.
21. MacFie 146 147	1917	not given	lymphatic leukemia	none apparently	malaria accidentally contracted	after malaria developed wbc fell from 286,000 to 5,000; patient moved away so end result unknown.	?
22. MacFie 146, 147	6/19	male 18	myelogenous leukemia	antimony intravenously	malaria accidentally contracted	wbc fell from 326,000 to 62,900 in 14 days; this effect rapidly effaced by quinine therapy.	?
23. Rudolph 217, 73	1925	male 14	myelogenous leukemia	none stated	malaria inoculated	one month after fever induced, wbc fell from 250,000 to 5,800 with normal differential; rbc increased from 1,500,000 to 3,800,000; hg from 24 to 52%; general condition greatly improved; spleen, lymph nodes decreased in size.	?
24. Gamble 73	1924	male 63	lymphatic leukemia	none stated	malaria inoculated intramuscularly; fever 105.6°F spiked 6 times in 3 weeks	febrile paroxysm 15 days after inoculation; wbc fell from 240,000 to 34,000 on day of last chill; no change in differential; rbc also fell from 2,460,000 to 1,520,000 during malaria, did not rise after quinine arrested it; lived 3 months after induced malaria.	death about 18 mos.
25. Gamble 73	12/25	male 27	myelogenous leukemia	none stated	malaria inoculated intravenously; (5 cc. of blood from case 24)	febrile paroxysm 13 days after inoculation; lasted 4 days; wbc fell from 750,000 to 204,000; quinine given 25 days after inoculation; duration improved blood picture brief; little change in rbc, and hg.	traced 12 mos. after inoculation; end result unknown

						decreased from 53% to 35%, differential reverted slightly toward normal; x-ray then given, followed by much more marked and lasting fall in wbc, to 8,700; rbc increased to 4,210,000, hg to 76%.	
26. Rosenow 209, 210, 213	1927 (?)	male 47	chronic myelogenous	x-ray with temporary clinical improvement	spiking fever to 103°F; malaria inoculated	first febrile paroxysm 6 days later; 5 in all before quinine given; wbc fell from 114,900 to 3,200 in 2 weeks; rose briefly to 89,000, then subsided to 34,000; rbc and hg also fell.	?
27. Huth 109	1948	male 10	paramyeloblastic	transfusions (ineffective)	severe phlegmon in region of biopsy; extensive fluctuation, abscess formation, entire right thorax, (staph. pyogenes aureus); high fever 4 weeks	in a most impressive fashion blood picture returned to normal 2 weeks after febrile period; 2nd sternal puncture then showed no leukemic cells in marrow.	?
28. Huth 109	1948	male 4	micromyeloblastic	transfusions given during infection	severe purulent mastoiditis, high fever (Escherichia coli); eye completely closed due to inflammation; mastoidectomy	wbc fell considerably during infection to 800; sternal puncture at height of infection showed normal conditions; Huth believed simultaneous administration aureomycin and transfusions during infection may have reinforced the remission; after relapse further administration of these agents did not cause further remissions.	death 4 mos. after infection
29. Huth 109	9/56	female 4	acute primary cell; almost moribund	none	severe pyocyaneous infection, pneumonia, bacterial endocarditis, myocarditis; erythema gangrenosum; profuse diarrhea, jaundice	complete remission for 3 months; after relapse 6-mercaptopurine given with further remission.	alive 1957

Author References	Date of Onset	Age Sex	Type of Leukemia	Type of Treatment Prior to Infection	Type of Infection Fever, Injection	Effect of Infection Fever, Injections	Period of Survival
30. Izar 111	1/29	male 53	chronic myelogenous	none	21 injections in 41 days, commercial preparation sulphur intramuscularly	spleen decreased markedly, pallor diminished, general condition improved, strength returned; thereafter rapid recovery, considered complete in 2 months; complete symptomatic cure lasted until Izar published case in 1931. (Note: this case may possibly have been a spontaneous remission, but since Izar is the only physician to publish the effects of sulphur therapy in leukemia and he obtained similar effects in other cases, it seemed worth including.)	alive about a year after injections; end result unknown
31. Larrabee	prior to 4/07	female 32	advanced myelogenous leukemia, cachetic, bedridden	Fowler's solution; 17 x-ray treatments	fever 105°F prior to toxin therapy; injections mixed toxins strep. and B. prodigiosus (Coley Toxins, XII) given intramuscularly; later few doses Tracy XI; also killed cultures B. coli communis	soon after injections begun spleen decreased markedly in size, general condition markedly improved, temperature normal in 4 days; color normal, gained weight; wbc fell from 128,400 to 20,000 in 6 weeks, only local inflammatory reactions noted from Type XII toxin, 2 very severe reactions from Tracy XI; less marked or prompt effect from B. coli; symptomatic recovery; still in remission when case published.	alive 1 year after onset; end result unknown
32. Larrabee	1907	male 59	advanced chronic myelogenous leukemia	untreated	pneumonia; injections mixed toxins as in case 31 given daily at first	tumors on forearms disappeared after pneumonia; 6 months later very ill; no improvement during first week toxin therapy; after first severe chill improved rapidly; dyspnea, cough ceased, spleen much smaller, cervical nodes decreased, area of dullness in left chest considered due to mediastinal nodes, disappeared; decrease in wbc; lasted 4 months.	end result unknown; alive when reported 4 ½ mos. after first injection

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