Benzene Exposure and Aplastic Anemia Followed by Leukemia 15 Years Later

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A painter who was exposed to benzene for 13 years developed a hypocellular bone marrow and pancytopenia. During the 15 years after recovery from aplastic anemia, there were found in the peripheral blood leukopenia, thrombocytopenia, and anemia. Night sweats, petechiae, splenomegaly, and pancytopenia prompted examination of the marrow, which was found to be characteristic of acute myelogenous leukemia.

ATOM BOMB VICTIMS have developed leukemia from 1 to 14 years, or longer, after exposure to irradiation.[1] With such a long induction period, clues to the elusive cause of leukemia may disappear years before the disease becomes manifest. The prediction that mothers who deliver large babies will probably have diabetes mellitus later in life provides a valuable opportunity for studying diabetes without being led astray by the effects of disturbed carbohydrate metabolism. Similarly, recognition that patients recovering from aplastic anemia may later develop leukemia gives one a chance to observe the so-called preleukemic period.[2-4] Preleukemia should be carefully described to facilitate investigation of stem-cell regulation before tbe anarchic leukemia state supervenes.

The patient whom we studied says that he was extensively esposed to benzene and later developed aplastic anemia; both conditions are associated with an increased risk of leukemia.[2-5] Blood counts obtained during a 15-year period after recovery' from the aplastic anemia revealed a persistent hematopathy which finally emerged as subacute myelocytic leukemia.

Report of a Case

Aplastic Anemia.—The patient, a 41-year-old house painter, entered Hines Veterans Administration Hospital on July 15, 1947, with complaints of anorexia, nausea, dark urine, light stools, fevers, and weakness for 1 week. As a house painter who worked inside, he had routinely thinned his paints with benzene for about 13 years.

His blood pressure was 130/90 mm Hg, his pulse, 120 beats per min. The skin and conjunctivae were icteric. There was gingivitis. The spleen, liver, and kidneys were not enlarged, but right upper abdominal tenderness was present. Initial blood counts were: hemoglobin level, 14 gm/100 cc; red blood cell count, 4,980,000/cu mm; and white blood cell count, 4,500/cu mm with 59% segmented neutrophils, 38% small lymphocytes, 2% monocytes, and 1% eosinophils (Fig 1). The urine was normal except that it contained bile. Direct serum bilirubin was 12.1 mg/100 cc, total bilirubin, 18.0 mg/100 cc. Alkaline phosphatase was 7.8 Bodansky units/100 cc. Icteric index was 101.2 units.

Choline chloride, vitamin B comples, and thiamine were given, but there was only slight improvement, after which the patient began bleeding from his gums. Blood counts were not changed much, but 2 weeks later, on Aug 20, 1947, when the bleeding persisted, the hemoglobin level was 10 gm/100 cc; red blood cell count, 3,600,000/cu mm; and white blood cell count, 1,300/cu mm, with 10% neutro-

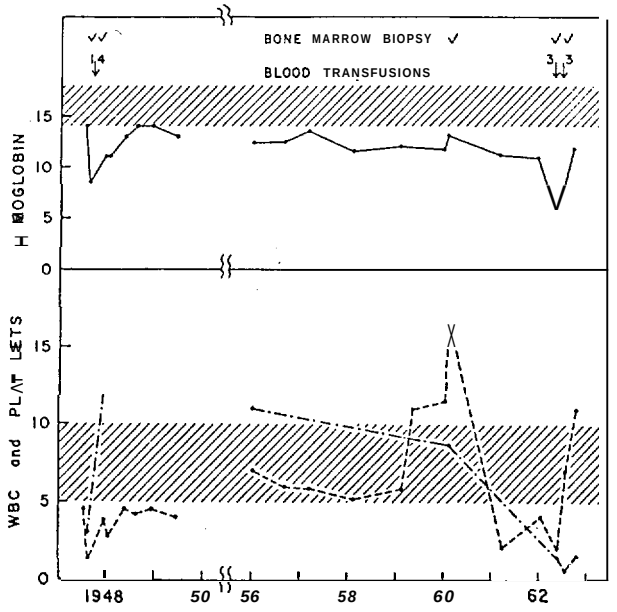

Fig 1.—Hemoglobin, leukocyte, and platelet counts from 1947 through 1962. Shaded areas at top and bottom represent the ranger of normal hemoglobin and leukocyte values respectively. Key: Hemoglobin level (gm/100 cc) solid line, leukocytes (10,000/cu mm) dashed line, and platelets (100,000/cu mm) dash-dot.

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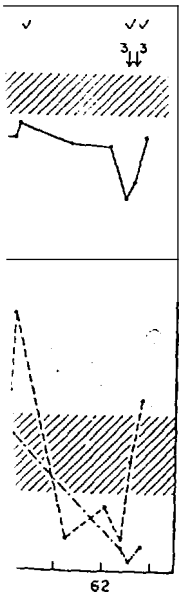

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Fig 2.—A section of bone marrow obtained by trephine biopsy of the sternum, on Aug 23, 1947, is hypocellular (× 350).

philS and 90% lymphocytes. There were only 30,000 platelets/cu mm. A bone marrow aspirate on Aug 21, 1947, was hypocellular. Defective maturation of both granulocytic and erythrocytic series was evident. In the former: the number of myelocytes equaled that of metamyelocytes and polymorphonuclear leukocytes; the polychrome normoblast was the predominant cell in the latter. Few blasts of any sort were seen. Megakaryocytes were scarce, but there were numerous lymphocytes, plasma cells, and fat-containing macrophages. A trephine biopsy of the sternum, obtained on Aug 23, 1947, revealed an estremely hypocellular marrow (Fig 2). The majority of cells occupying a few small foci of reticular proliferation were nongrnnular mononuclears resembling large lymphocytes and plasma cells. A few isolated groups of two to three normoblasts and granulocytes were present. No tubercles were found. Dr. George V. LeRoy, the hematological consultant, concluded that the patient had developed aplastic anemia after exposure to benzene while convalescing from severe hepatocellular jaundice.

Consistent with Dr. LeRoy's recommendations, the patient was given 14 pints of whole blood during the nest 4 weeks. Extract of yellow bone marrow (one ampule daily) was given intramuscularly for about 10 weeks. Penicillin, 30,000 units every 3 hours, was given during the first week. Bleeding from the gums stopped after the 4 weeks of blood transfusions. A bone marrow aspirate on Oct 4, 1947, provided evidence of early, but not *too* successful, marrow regeneration, according to Dr. LeRoy's interpretation. No nucleated erythrocytic cells were seen in the hypocellular marrow: Lymphocytes and mononuclear cells described as the "monocytoid leukocytes of Downey" were predominant. Despite low blood counts, the patient seemed sufficiently recovered to be discharged on Dec 31, 1947.

'Subsequently the patient was given liver and iron injections and examined periodically in the outpatient department. He felt well and had no recurrence of bleeding. Hemoglobin values reached the lowest limit of normal, but mild leukopenia was constant. Anemia and leukopenia were still present on the last blood counts obtained at Hines Hospital on June 16, ,1949 (hemoglobin level 13.0 gm/100 cc, white blood cell count 4,000/cu mm).

Preleukemic Period—No more blood counts were available until 1956, when the patient came to the University of Chicago Clinics complaining of belching and lower abdominal cramps. Except for a scar over his sternum and a grade 1/6 apical systolic murmur, his examination was normal. Anemia and mild thrombocytopenia were present. During the next 4 years, while the patient was treated with a bland diet and phenobarbital for an irritable colon, a persistent anemia was apparent from periodic blood counts.

One neutrophilic myelocyte, two metamyelocytes, and normoblasts were reported on the peripheral blood film on Jan 23, 1960. The bleeding time from an ear puncture extended beyond 15 minutes. On Feb 9, 1960, the day of the patient's first University of Chicago Hospitals admission, the liver was palpable two finger-breadths below the right ribs, but the spleen was not palpable. The left ear was red and swollen. Anemia, thrombocytopenia, and leukocytosis were present. No immature cells were seen on several blood film examinations while the patient was in the hospital. Increased mature granulocytes accounted for the elevated myeloid-erythroid ratio noted on the section of bone marrow aspirate obtained on Feb 11, 1960. Cellularity, maturation, megakaryocytes, and stained iron were all normal *(Fig 3)*.

After his discharge, the patient returned to work every day as a drill-press operator. He seemed healthy, but admitted that he bruised with slight trauma and that spontaneous bruising occurred. Routine blood counts on March 4, 1961, demonstrated leukopenia and anemia. Fourteen months later, a personal physician told the patient *that* he was severely anemic and recommended that he return to the University of Chicago Hospitals.

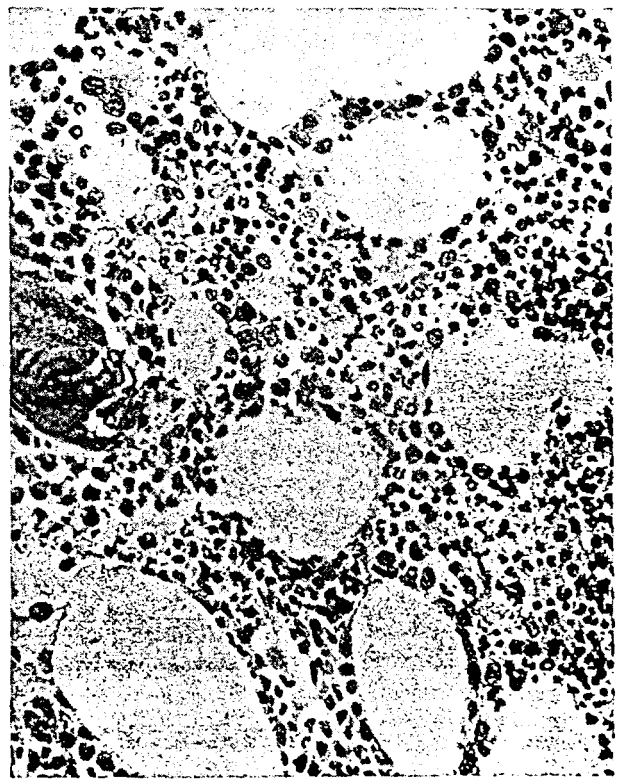

Fig 3.—A section of sternal bone morrow obtained by needle biopsy, on Feb 11, *1960*, shows normal cellular maturation and megakoryocyter (× 3501.

Leukemia—On his second admission, May 17, 1962, the patient told of, recent nose bleeds, and ecchymoses were found on his arms, chest, and legs. The heart was slightly enlarged. The spleen was firm 3 cm below the left ribs. A nontender, firm liver extended 10 cm below the right ribs. Initial blood counts were: hemoglobin level, 7.4 gm/100 cc; hematocrit level, 24%; red blood cell count, 2,190,000/cu mm; and white blood cell count, 2,700/cu mm, with 31% segmented neutrophils, 53% lymphocytes, 3% monocytes, 6% myeloblasts, 1% promyelocytes, 5% neutrophilic myelocytes, and 1% metamyelocytes. There were 7 normoblasts per 100 leukocytes. Subsequent counts: reticulocytes, 5.7% red blood cells/cu mm; and platelets, 15,400/cu mm. Sections of bone marrow aspirate obtained on May 22, 1962, contained hypercellular marrow in which the myeloid-erythroid ratio was increased 10 to 1. Arrest of maturation in the myeloid series was evident from the predominance of myeloblasts and promyelocytes and a paucity of metamyelocytes and segmented neutrophils. Normoblasts were present. Megakaryocytes were rare. Prussian blue stained iron was abundant. A serum protein electroghorectic pattern was devoid of evidence of protein abnormality, including a "myeloma spike." A gastric aspirate contained hydrochloric acid. Plasma iron was 110 μg/100 cc; unsaturated iron binding capacity was 150 μg/100 cc. Plasma clearance of Fe^{59} was about twice as rapid as normal. Ninety per cent of the injected radioiron appeared in the erythrocytes in 3 days, in contrast to a normal range of 60% to 70% in 7 days. Uric acid (enzymatic method) was 6.4 mg/100 cc. Type A hemoglobin was detected by electrophoresis.

The patient was afebrile, and except for several days of bleeding from his sternal puncture, he felt moderately well. He received 3 units of blood, and because of thrombocytopenia and probable hemolytic anemia, 30 mg of prednisone daily was begun several days before he left the hospital.

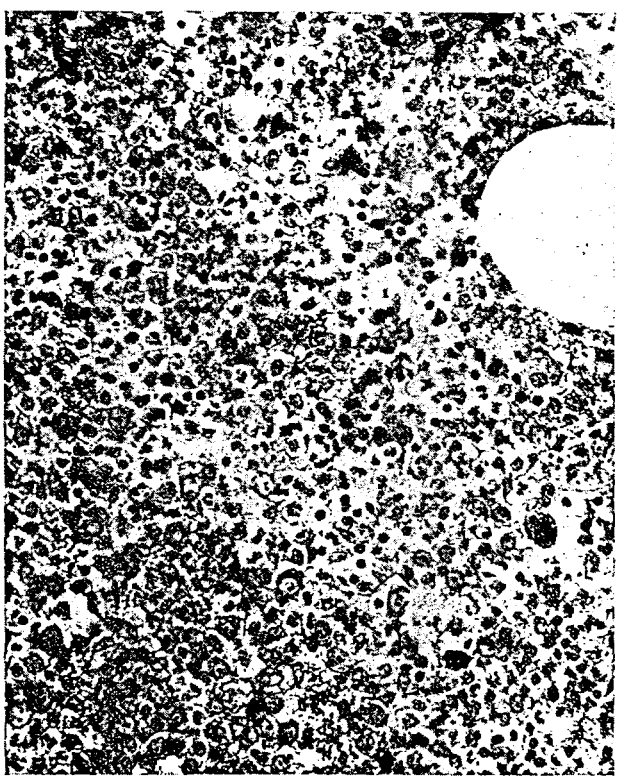

Fig 4.—A section of sternal bone marrow obtained by needle biopsy, on July 30, 1962, is frankly leukemic. Sheets of myeloblasts replace normal marrow cells except for some normoblasts (× 375).

The hematologists considered subacute myelogenous leukemia the most likely diagnosis.

The patient returned to his work, taking 30 mg of prednisone daily. He experienced easy bruising and more frequent night sweats, and on July 27, 1962, the discovery of recurrent anemia (hemoglobin level 7.4 gm/100 cc) and thrombocytopenia (6,000 platelets/cu mm) prompted readmission to the hospital. Immature cells were seen in the peripheral blood. Petechiae were present in the skin and mucus membranes. The spleen was palpable 5 cm below the costal margin, and the liver extended 6 cm below the right ribs. Sternal bone marrow aspiration was performed on July 30, 1962, and sections were prepared. Sheets of immature cells with pale-staining nuclei resembling the myeloblasts of the previous sections occupied 90% of the marrow (Fig 4). No mature leukocytes were seen (leukemic hiatus). Normoblasts were diminished, and megakaryocytes were rarely found: The marrow was unquestionably leukemic. The patient was transfused with 3 units of blood and discharged with a diagnosis of acute myelogenous leukemia. Blood counts in the outpatient department have shown persistent anemia and thrombocytopenia.

The patient got along fairly well taking prednisone until January, 1963, when leukocytosis ranging from 95,000 to 146,000 leukocytes per cu mm (mostly myelocytes and myeloblasts) occurred. There was transient improvement while the patient took mercaptopurine. However, he died on April 24, 1963, with a gram-negative bacterial pneumonia and septicemia despite treatment with antibiotics, mercaptopurine, prednisone, and blood transfusions.

Comment

Extensive exposure to benzene preceded a persistent hematological abnoimality starting with, as far as we know, a hypocellular bone marrow and pancytopenia which was followed by a nearly normal bone marrow with variable leukopenia, anemia, and thrombocytopenia. Finally, after 15 years, a frankly leukemic marrow and pancytopenia were found. It is tempting to relate the blood diseases, or disease, to benzene exposure.

Benzene poisoning is not an invariable sequela of chronic benzene exposure,[6] but, when poisoning has occurred, the bone marrow varies from severe hypoplasia to extreme hyperplasia.[1] The first signs of poisoning may appear with an infection, long after exposure has stopped.[5] Our patient's hepatitis may have resulted from either benzene or a virus.

Acute leukemia has occurred after benzene poisoning in several instances;[2-4, 9] one patient died with acute leukemia after 23 years of exposure to benzene.[1] Furthermore, leukemia has developed in patients who have previously had hypocellular bone marrow.[2-4, 9]

The duration of a preleukemic phase in our patient cannot be determined because no blood counts are available from June, 1949, to January 1956. From 1956 until May, 1962, when the diagnosis of leukemia was made, his course was characteristic of preleukemia as Block and others have described it.[7] There was evidence of a hemorrhagic tendency, and thrombocytopenia was present when platelets were measured. Leukopenia and anemia were also present, although not always simultaneously. In describing a patient who developed leu-

kemia 9 years after the beginning of a prolonged hematological disorder, Williams observed an initially hypocellular marrow; a preleukemic period characterized by anemia, neutropenia, and thrombocytopenia, and finally, the subsequent development of a hyperplastic marrow and myeloblastic leukemia.' Although the maximal risk of leukemia occurred 4 to 7 years after the atomic explosion in Japan, the incidence of leukemia was decidedly increased in exposed persons 14 years after the blast,' a latent period similar to that described in this study. The leukemia rate in Japan ordinarily is 20 to 30 cases per million people each year. The 1958 leukemia rate in persons exposed within a 1,500 meter radius of the blasts in Hiroshima and Nagasaki exceeded 450 cases per million.'

If benzene poisoning caused this patient's blood disease, one might speculate at great length concerning the manner in which the delicate control of stem cell proliferation and maturation was perverted. As recognition of the preleukemic phase becomes more assured, the study of stem cell kinetics during that period will undoubtedly prove more rewarding than are present attempts to identify the cause of a leukemia during its end stages.

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Dr. Clifford W. Gurney helped in studying the patient; Drs. Stanley Yachnin and George V. LeRoy offered suggestions concerning the patient's treatment; Dr. Armand Littman provided the patient's old records.

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Generic and Trade Names of Drugs

Choline chloride—Choline *Chloride.*
Prednisone—Deltasone, Deltra, *Metacorten, Paracort.*

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PREVENTIVE HYGIENE SUGGESTIONS OF 1915.—But we have not yet even begun to demand that study and care of the individual which is . . . fundamental. We have as yet paid little or no attention to over-eating, over-working, over-drinking, deficient exercise, deficient sleeping, family hygiene, and the hygiene of special organs, such as eyes, ears, bowels, nose and feet, all of which I propose to group together under the term preventive hygiene. We have achieved much in preventive medicine and preventive sanitation, but we have as yet failed for the most part in preventive hygiene, which is perhaps the most important of all. Here, therefore, we may reasonably expect the greatest progress in the nearest future. Rightly studied, preventive hygiene will include personal, domestic, family and social hygiene. It will deal with celibacy and marriage, with housekeeping, with the high cost of living, with food economy, with domestic service, with child hygiene, and with the right conduct of mature and elderly life, as well as with personal hygiene. It will in the future play, perhaps, the principal part in solving many of the problems of American life, health, prosperity and happiness. Our teaching of physiology, both on the higher levels and the lower, has never emphasized as much as it should have done its practical hygiene applications to the conduct of life. In fact, our whole teaching of hygiene and sanitation has been grossly neglected. Even the best medical schools have paid but scant attention to these subjects, while the instruction given in our public schools has generally suffered from half-informed teachers and uninformed school committees. The best teaching of today is to be found, not in the text-books or the schools, but in the leaflets and booklets of certain boards of health and life insurance companies. This, surely, is a scholastic reproach which must not be allowed to stand.—Sedgwick, W. T.: American Achievements and American Failures in Public Health Work, ***Science,*** July-Dec, 1915.