unaltered disposition of glucose despite concurrent elevations of plasma insulin are interpreted as consistent with peripheral resistance to insulin during late pregnancy. Contrainsulin factor or factors of a lipolytic nature have been implicated. The metabolic interactions are designated as a form of "accelerated starvation," and the parasitization of maternal glucose and gluconeogenic precursors by the conceptus is emphasized.

It is postulated that the contributions from contrainsulin factors would be additive to the effects of intraplacental insulin degradation in the gestational challenges to maternal insulin economy.

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BENZENE AND LEUKEMIA*

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HYPOREGENERATIVE and aplastic types of hemopathy brought about by exposure to benzene were described in the nineteenth century, and the question of leukemic myelosis from the same cause has been debated since the first description of a case of leukemia referred to the action of benzene.[1]

A paper by Cronkite[2] (1961) summarizes the natural history of "benzene leukemia." From this and other American papers on benzene poisoning it seems that the European and especially the Italian literature on benzene leukemias is poorly known. Therefore, we thought that it would be of some interest to give a short account of the cases of leukemia attrib-

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exposed to benzene in Italy, with special emphasis on those seen at the Clinica del Lavoro of the University of Milan.

In 1938 Penati and Vigliani[3] reviewed the available world literature on benzene myelopathy and pointed out that, in some cases, the pathology hardly bore out the diagnosis of aplastic myelosis — that is, hyperplastic bone marrow and leukemoid reaction.

Although all types of leukemia have been attributed to benzene, many cases reported between 1928 and 1938 lack reliable data on exposure to benzene.

Since 1941, 13 cases of "benzene leukemia" have been reported in Italy, besides the cases of the Clinica del Lavoro of Milan and the Institute of Occupational Health of Pavia, which will be considered later.

Of these 13 cases, 9 were hemocytoblastic (or myeloblastic, according to Naegeli's terminology) in type. The remainder were chronic myeloid leukemia (1 case), erythremia (2 cases) and erythroleukemia (1 case). In all cases in which a history of prolonged and severe exposure to benzene could be obtained, the leukemia was hemocytoblastic in type, often preceded by a period of apparently aplastic anemia with leukopenia.

In the province of Pavia many cases of chronic benzene poisoning arose from the use of glues containing benzene in the manufacturing of shoes. Shoes are manufactured in many small factories, and very often also at workers' homes. The Institute of Occupational Health of the University of Pavia saw in the last three years 41 cases of chronic benzene intoxication with hemopathy. Five of them were leukemias — more precisely, 3 hemocytoblastic, 1 paramyeloblastic and 1 myeloblastic. All these cases came from factories where cases of aplastic anemia also occurred and where the glues contained a high percentage of benzene. According to the determinations of benzene vapor carried out in some factories, workers with glue were exposed to concentrations well above the maximum allowable value.

Cases Seen at the Clinica del Lavoro

Between 1942 and 1963 we observed 47 patients with benzene hemopathy. Two showed anemia, 7 anemia and leukopenia, 5 anemia and thrombocytopenia, 26 pancytopenia, 6 leukemia, and 1 leukemoid reaction.

We present the clinical and laboratory details of the 6 cases of leukemia.

Case 1.* M.G., a 49-year-old man, entered a leather-cloth factory in 1933 as a spreader and calender operator, applying resins dissolved in benzene and acetone. Working conditions were bad, and many workers had fallen ill with anemia. After 1 year the patient complained of asthenia and pallor, with mucosanguineous diarrhea, and from 1938 to 1940, he had repeated epistaxis. His condition worsened, and he was admitted to our department in January, 1942.

Physical examination showed pallor, an enlarged liver and a spleen palpable 2 fingerbreadths below the left costal margin.

Examination of the blood revealed a red-cell count of 1,410,000, with a hemoglobin of 34 per cent (Sahli), and a white-cell count of 4800, with 19 per cent hemocytoblast forms (including many microhemocytoblast forms), and occasional neutrophilic myeloblast forms, promyelocytes and myelocytes. The platelet count was 56,000. Sternal-marrow puncture yielded 71 per cent hemocytoblast forms, of which 36 per cent were microhemocytoblast forms.

No improvement occurred in spite of treatment. Hemorrhages, fever and leukocytosis (white-cell count of 34,000, with 50 per cent hemocytoblast forms) supervened, and death followed after 1½ months.

Case 2.† In 1940 R.F., a 38-year-old man, became an assistant operator in a rotogravure firm, where the inks contained 40 per cent benzene. The benzene concentration in the department where he worked varied between 0.60 and 2.10 mg. per liter. Asthenia and pallor developed in 1944. He had pain in the bones, with fever, in 1945, when he entered the Clinica with pallor, slight splenomegaly and some ecchymoses and petechiae.

The red-cell count was 1,450,000, with a hemoglobin of 38 per cent (Sahli), and the white-cell count 3700, with 9 per cent hemocytoblast forms and some immature myelocytes; the platelet count was 50,000. The red-cell count fell to 800,000, and the white-cell count to 2200, with 33 per cent hemocytoblast forms, mostly micro forms. The spleen enlarged to the transverse umbilical line, and there were diffuse hemorrhages. The patient died in May, 1945. Post-mortem findings were myeloid (hemocytoblastic) metaplasia of the liver and spleen; the sternal, costal and vertebral bone marrow was atrophic. Other cases of benzene anemia and a case of leukemia (Case 4) occurred in the same factory.

Case 3. T.S., a 29-year-old man, for 8 years was a spray varnisher with nitrocellulose varnishes dissolved in solvents containing 60 per cent benzene. In 1956 he began to complain of asthenia and loss of appetite. In July, 1958, high fever and diffuse pain in the bones developed. Our diagnosis was hemocytoblastic leukemia with leukopenia. Remission followed treatment with cortisone. In November, 1958, his condition appeared fairly good: the spleen was scarcely palpable; the red-cell count was 4,800,000, with a hemoglobin of 90 per cent (Sahli), and the white-cell count 47,800, with 5 per cent hemocytoblast forms and numerous neutrophilic myelocytes and metamyelocytes; the platelet count was 150,000. Sternal-marrow puncture revealed a high concentration of hemohistioblast and hemocytoblast forms.

On treatment with 6-mercaptopurine and prednisone the white-cell count fell to 3600, with a few myelocytes and metamyelocytes. Cessation of antimetabolites was followed in a short time by a rise in the count to 200,000, with 64 per cent hemocytoblast forms, which could be controlled by renewed treatment with 6-mercaptopurine. The patient was discharged in a satisfactory condition with a good hematopoietic response, a normal white-cell count and very few hemocytoblast forms. He was then lost to follow-up study.

Case 4. At 24 years of age, in 1938, M.A. began to work in the same rotogravure department as Case 2. In 1945, when his mate, R.F., died from benzene leukemia and other workers also had signs of benzene poisoning, this man was not examined. During 1949 he showed a slight tendency to leukopenia (count of 4000) and relative neutropenia (count of 50 per cent). After 1949 benzene was replaced by toluene, xylene, hexane and organic acetates, and no further cases of benzene poisoning have since been found. In the course of routine examinations M.A. was seen every 3 months and was reported normal until February, 1961, when he began to complain of asthenia, sporadic bouts of fever and pallor. In March the red-cell count was 1,600,000, with a hemoglobin of 29 per cent (Sahli), and the white-cell count 30,000, with 81 per cent hemocytoblast forms, mainly of the micro type. Sternal-marrow puncture gave evi-

*Previously reported by Vigliani and Saita.[1]

†Previously reported by Saita.[2]

dence of morphologically similar cells of hemocytoblastic type, with rare occurrence of granuloblastic and erythroblastic types. The platelet count was 83,000; the coagulation time (Howell method) was prolonged, and prothrombin utilization was markedly reduced.

Transfusion, prednisone and 6-mercaptopurine led to marked improvement; by May, 1961, the red-cell count was 4,200,000, with a hemoglobin of 80 per cent (Sahli); and the white-cell count 10,000, with rare hemocytoblast forms (3 per cent), neutrophilic myelocytes and metamyelocytes.

Examination in February, 1962 (over a year after discharge from the hospital), after a relapse, showed a red-cell count of 2,000,000, with a hemoglobin of 30 per cent (Sahli), and a white-cell count of 83,000, with 58 per cent hemocytoblast forms and very few platelets. The patient had hemorrhagic and feverish bouts. Treatment with antibiotic transfusions, prednisone and 50 mg. of 6-mercaptopurine per day led to another transitory remission (white-cell count of 4000, with 22 per cent hemocytoblast forms), but fever reappeared, with bronchopneumonic foci at the lung bases and a rise in the white-cell count to 63,000, with 57 per cent hemocytoblast forms, many of which were very atypical. At no time was either splenomegaly or lymphadenopathy discovered. Death occurred in April, 1962, more than 1 year after the clinical appearance of the disease. No autopsy was performed.

CASE 5. M.A., a 50-year-old man, from 1943 to the spring of 1962 had a job of sticking rubber ribbons in the edge of billiards with glue containing pure benzene, spread on the ribbons with a pencil. He did this work for 2 or 3 hours a day. After the spring of 1962 the benzene in the glue was replaced with a nonaromatic solvent. In November, 1961, he experienced fever, asthenia and pallor; in June examination of the blood in a town hospital showed a red-cell count of 2,650,000, with a hemoglobin of 50 per cent (Sahli), and a white-cell count of 2000, with 20 per cent neutrophils and 80 per cent mononuclear leukocytes; sternal-marrow puncture disclosed many atypical hemocytoblast forms and very few normal cells of the red and white series. He improved considerably with blood transfusions and corticosteroids and was discharged in good condition. A checkup at the Clinica del Lavoro in January, 1963, showed a red-cell count of 3,900,000, with a hemoglobin of 83 per cent (Sahli), and a white-cell count of 3900, with 42 per cent neutrophils, 4 per cent eosinophils, 48 per cent lymphocytes and 6 per cent monocytes; the platelet count was 60,000. Sternal-marrow puncture showed a normal bone marrow, with only a slight increase of basophilic erythroblast forms. During that winter the white-cell count fell progressively to 2500, and the neutrophils to 14 per cent, but no immature forms were seen in the circulating blood. At the beginning of March bouts of fever appeared, and the count fell to 600, with 15 per cent hemocytoblast forms, 1 per cent myeloblast forms, 5 per cent neutrophils, 78 per cent lymphocytes and 1 per cent monocytes. Sternal-marrow puncture disclosed very few cells, mostly of the hemocytoblast type. Corticosteroid treatment was started; the white-cell count remained between 1600 and 2400, and the hemocytoblast forms in the blood smear between 5 and 32 per cent, with no other immature form. Platelets diminished to the positivity of vascular fragility tests; the red-cell count was 2,800,000, and the hemoglobin 60 per cent (Sahli). At the end of April the patient went home and was lost sight of. At no time was enlargement of the spleen or lymph nodes noticed.

CASE 6. L.A., a 53-year-old woman, was an artificial-flower maker for 3 years, using a glue dissolved in a solvent containing 25 per cent benzene. In June, 1963, she had weakness, nausea and pallor. On admission to our department, examination of the blood showed a red-cell count of 1,800,000, with a hemoglobin of 40 per cent (Sahli), and a white-cell count of 2800, with 30 per cent neutrophils, 2 per cent eosinophils, 65 per cent lymphocytes and 3 per cent monocytes, with no pathologic cells; there were 16 erythroblast forms for every 100 white cells. The platelet count was 110,000. Sternal-marrow puncture gave a normal pattern except for a high number of mitoses. This hypoplastic anemia was treated with repeated blood transfusions. In October there were attacks of fever, with a maximu temperature of 102.2°F (39°C.). On October 20 the whit cell count was 51,000, with 4 per cent hemocytoblast an 8 per cent myeloblast forms, 14 per cent myelocytes, 4 p cent metamyelocytes, 29 per cent neutrophils, 2 per ce eosinophils, 1 per cent basophils, 13 per cent lymphocyt and 25 per cent neutrocytes. The hemocytoblast and myel blast forms showed atypical features, with large cytoplas and monocytoid nucleus. A total of 3 normoblast forms f every 100 white cells were seen. Sternal-marrow puncti performed on October 24 showed that almost all cells the marrow were hemocytoblast and myeloblast forms.

The patient's condition deteriorated rapidly in spite therapy with 6-mercaptopurine and prednisone, and she di on October 28 with large pharyngeal and buccal ulce The spleen was never palpable. Autopsy demonstrate complete leukemic metaplasia of the spleen, with leuken infiltrations of the liver, lymph nodes, kidneys, colon, lun and brain. The leukemic cells looked like undifferentiate stem cells.

Discussion

The attribution of the cases seen at the Clinic del Lavoro to the exposure to benzene cannot b doubted. Cases 2 and 4 occurred in the same worl shop, and both patients were exposed to concentr tions of benzene ten times greater than the maximu allowable values generally accepted. In Cases 1, and 4, which occurred in factories where other wor ers were affected, aplastic or hyporegenerative hemo athy developed. Cases 3 and 6 handled a dilue containing a dangerous percentage of benzene. Ca 5 handled a glue dissolved in pure benzene.

The following significant points are worth emphasi

Hematologically, the 6 cases described were sir ilar. They were all hemocytoblastic leukemias wit sometimes, absence of elevated white-cell count moderate or absent splenomegaly, thrombocyt penia and invasion of the bone marrow by inte sive hemocytoblastic proliferation. Thus, the pi ture was one of undifferentiated stem-cell leuk mia, with myeloid characteristics as shown, for e ample, by a positive peroxidase reaction.

Leukemias of this kind, even a few years ag ran an acute or a subacute course, with, at mos a few weeks' survival. The terminal septic an hemorrhagic phenomena today can be prevent by medicinal means so that fairly long remissio have been obtained in some cases.

It is known that microhemocytoblastic leuk mias are especially sensitive to the folic ac antagonists, to antimetabolites and to cortisone, fact that may explain the longer and more fr quent remissions of infantile leukemia in whic microhemocytoblast forms are more prevale than in adult cases. On the other hand, hemo cytoblastic leukemia with extremely large or aty ical cells is less responsive to these therapeut measures. Cases 3 and 4 showed many microh mocytoblast cells, with few atypical or large-size cells. In Case 4 the latter appeared in large nur bers only in the terminal stages. Case 6 had a rapid course, probably owing to the highly atypic

aspect of the hemocytoblast (parahemocytoblast and paramyeloblast) forms, with an abundance of monocytoid cells in the circulating blood.

Five of the patients had low white-cell counts at the outset that were independent of any therapy. In Cases 2 and 5 leukopenia was a feature throughout, and we consider it probable that the leukopenia may have escaped us in Case 4. This finding leads us to think that leukopenic leukemia may not be an infrequent feature of benzene hemocytoblastic leukemias, leukocytosis being the terminal phase in many cases.

In Case 6 benzene leukemia was preceded by a hyporegenerative or aplastic phase. Such an event also occurred in some cases seen at the Institut of Occupational Health in Pavia and in the case described in the United States by De Gowin[9] in 1963. It is possible that many more cases of leukemia developed on a background of aplastic anemia.

Thus, Case 1 complained for eight years of pallor and sporadic epistaxis. Case 3 was asthenic for two years. Case 2 showed diffuse atrophy of the bone marrow (sternal, costal and vertebral). Case 4 had mild leukopenia and neutropenia for twelve years before the late appearance of the leukemia.

The particular aspect of these cases, in which the onset of a frank leukemia was preceded by a preneoplastic, hyporegenerative phase, may be better understood in the light of an investigation carried out recently by Pollini and Colombi[8] in 6 cases of human aplastic anemia due to benzene, 1 of which had a fatal outcome. They cultivated the cells obtained by sternal puncture, and observed the mitoses blocked in the metaphase by means of colchicine. Then they mapped the chromosomes of 342 dividing cells and saw that 70 per cent of the cells showed abnormalities in karyotype. The large metacentric chromosomes of the first two groups of the Denver classification gave evidence of deletions; polyploidism was limited to a few cells. Some other cells showed structural chromosomal changes, as the presence of a chromosome D, or chromosomal fragments, or supernumerary chromosomes. This finding suggests a mutagenetic effect of benzene on the blood cells, and may help to explain the appearance of leukemia during the course of a benzene hypoplastic anemia. Actually, it is known that leukemic cells, especially the most undifferentiated, often possess an abnormal karyotype. It would be interesting, and perhaps rewarding, to undertake a systematic study of the chromosomes of the bone-marrow cells in chronic benzene poisoning and to follow clinically and hematologically the patients with altered chromosome pattern.

We have never seen a case of chronic myeloid or lymphatic leukemia in workers poisoned with benzene: all cases seen by us and at the Institute of Pavia, in which harmful and prolonged exposure to benzene vapors was ascertained, were hemocytoblastic in type. Whether chronic types of leukemia can be induced by benzene is still an open question, but we must emphasize our view that in some of these cases reported in the literature the occupational history was not convincing. The number of persons occasionally exposed to benzene or exposed to very low benzene concentrations was so high that some cases of chronic leukemia could have occurred among them as among any other working population.

We are fully aware of the fact that no final statement about the existence of a true "benzene leukemia" may be made, without a statistical analysis of the incidence of leukemia among workers exposed to benzene as compared with that among a control group of the same age, sex and living habits. Unfortunately, this analysis is particularly difficult in our cases because of the large number of shoe and other factories handling benzene, the artisan work carried out at home by many factory-employed workers and the frequent and unsuspected changes in benzene content of the glues and solvents used by the workers.

In the biennial period 1959-1961 the incidence of all forms of leukemia among the general population of Milan was 0.01 per cent: 46 per cent of these were acute leukemias, 28 per cent chronic myeloid leukemias and 26 per cent chronic lymphatic leukemias. Thus, each year 1 case of acute leukemia occurred among 20,000 people.

There is reason to believe that in the Milan and Pavia provinces no more than 5000 workers were exposed to contact with benzene and probably less than 3000 were exposed to dangerous concentrations of benzene vapors.

According to the statistics of the National Institute for Insurance against Accidents and Occupational Diseases from January, 1960, to December, 1963, cases of blood dyscrasias due to chronic benzene poisoning occurred in the provinces of Milan and Pavia as shown in Table 1.

The incidence of acute leukemias in 1962-63 showed a sharp rise, coinciding with the increase in the number of cases of benzene intoxication, and was about twenty times higher than expected,

TABLE 1. *Blood Dyscrasias Due to Chronic Benzene Poisoning in the Provinces of Milan and Pavia, 1960-1963.*

YEAR	NO. OF CASES	NO. OF DEATHS	ANEMIA		LEUKEMIA	
			NO. OF CASES	NO. OF DEATHS	NO. OF CASES	NO. OF DEATHS
1960	4	1	4	1	0	0
1961	7	2	6	1	1	1
1962	36	11	31	7	5	4
1963	21	12	15	6	6	6
Totals	68	26	56	15	12	11

even assuming that 5000 people were exposed to benzene. Moreover, if one considers the cases of benzene poisoning that actually occurred, 11 cases of leukemia among 68 of blood dyscrasias cannot be overlooked. The incidence of leukemia is even more striking if one considers the fatal cases: out of 26 deaths, 11 were due to leukemia, and 15 to aplastic anemia.

Our figures correspond fairly well to those collected in France by Cavignaux[5]: according to him, during 1960-61, 42 cases of benzene myelopathy occurred, 25 in men and 17 in women; 6 of these 42 cases were leukemias. From 1947 to 1961, 45 fatal cases of chronic benzene poisoning were recorded in France: 15 patients had acute leukemia, 22 aplastic anemia, and 2 lymphatic and 6 myeloid leukemia. These data point out the high incidence of leukemias among the cases of benzene poisoning in France and the prominent position of acute stem-cell leukemias among the cases of leukemia attributed to benzene. It may be interesting to compare the action of benzene and of ionizing radiation in producing leukemia; they seem to stand in contrasting position in that the former more readily causes the acute hemocytoblastic type, and the latter the chronic myeloid type.

Our Case 4, with a latent period of twelve years after cessation of exposure to benzene, does not permit us to attribute the disease to persistence of benzene in the bone marrow. A similar case, with a latent period of fifteen years, was recently presented by De Gowin.[6] On the basis of the initiation-promotion theory of the induction of neoplasms, we might regard benzene as an initiator of the leukemia process, but we have no suggestion of a possible promoter.

Hyporegenerative and pancytopenic types of hemopathy are more frequently associated with benzene than the hyperplastic-anaplastic types. The cases of hypoplastic hemopathy are almost always reversible. In our series of 31 cases of involutional myelopathy, only 2 were fatal, and 1 of these from complicating typhoid. Leukosis, on the other hand, is always fatal. We suspect that, formerly, many fatal cases diagnosed as acute or subacute hemorrhagic aleukia were really cases of acute leukopenic or aleukemic leukemias.

Summary and Conclusions

In the last twenty years 47 cases of benzene hemopathy have been seen at the Clinica del Lavoro of Milan; 40 were hypoplastic in type, and 2 of them were fatal. Six were hemocytoblastic leukemia. No case of chronic typical myeloid or lymphatic leukemia was seen.

Two of the 6 cases of leukemia, seen in 1942-45, were rapidly fatal. Three of the remainder, seen recently, were treated with corticosteroids and with 6-mercaptopurine and showed remissions. These favorable responses to modern therapy may have been due to the presence of microhemocytoblast forms and to the scarcity of atypical cells: in the patient who died rapidly in spite of the therapy, the hemocytoblast cells were grossly atypical.

Attention is called to the initial leukopenia in benzene leukosis and the frequency of hyporegenerative or aplastic stages before the development of frank leukemia.

In 1 of the 6 cases, the leukemia appeared twelve years after cessation of the exposure to benzene.

A summing up of the cases of benzene myelopathy seen at the Institute of Occupational Health of Pavia and in France shows approximately the same incidence of leukemias (12 to 13 per cent) as seen at our institute and the high prevalence of stem cell (hemocytoblastic and myeloblastic) types.

Leukemia, mainly hemocytoblastic or myeloblastic in type, may be due to the action of benzene. Great caution must be exercised before admitting the benzene etiology of chronic myeloid or lymphatic types of leukemia.

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