CHRONIC EXPOSURE TO BENZENE (BENZOL). III. THE PATHOLOGIC RESULTS*†

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ALTHOUGH benzene poisoning was recognized as early as 1897 by Santesson (42) and its pathogenesis was to a large extent elucidated by the classic experimental and clinical studies of Selling (46, 47) from 1910 to 1916, the paucity of pathologic studies of human material has repeatedly been noted (7, 19, 20). A considerable body of experimental evidence has, it is true, served to some extent to offset this lack (2, 12, 21, 22, 27, 28, 30, 34, 35, 45, 47, 53, 54), but has in general been limited to the effects of acute poisoning, whereas the human disease is preeminently chronic in character. Dispersion of material has unquestionably prevented any one pathologist from studying a considerable group of cases, and incompleteness of most case reports from the pathologic point of view has rendered surveys relatively inadequate. The present collection of 19 cases with prolonged exposure to benzene from which histologic material is available therefore permits a broader perspective of the anatomic features of the human disease than has heretofore been possible.

It is probably not unfair to assume that the present consensus regards chronic benzene poisoning as typically manifested by the syndrome of aplastic anemia—a syndrome characterized hematologically by severe refractory anemia, leucopenia, thrombocytopenia and the usual clinical signs and symptoms which accompany such disorders of the blood picture such as weakness, pallor, purpura and extreme susceptibility to infection. As the underlying basis for such a condition, aplasia of the bone marrow has unquestionably been generally assumed. That such a picture in the peripheral blood does not, however, necessarily indicate an aplastic marrow has been recognized by numerous observers in recent years. Blumer (3), Thompson, Richter and Edsall (49), Rhoades and Miller (38) have presented abundant evidence that the presumption of an aplastic marrow is not always warranted under such conditions. In fact relatively few of the cases cited by these authors

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† The substitution by the editorial staff of the journal of the synonym *benzene* for the *benzol* of our original manuscripts is unanimously deprecated by the authors, though it has the sanction of such organizations as the American Chemical Society and the American Medical Association. In present day usage (Webster's unabridged dictionary) benzene refers to the chemically pure product, benzol to the ordinary commercial one. It is to the latter that the individuals reported upon in these papers were exposed.

Control of poisoning with this agent requires education of the layman and the use of a term readily confusable with the relatively harmless agent benzine, when a word is available which obviates all possible confusion, seems to us unfortunate.

showed any diminution of bone marrow activity, whereas the majority exhibited marked medullary hyperplasia. In benzene poisoning, also, hyperplasia of the bone marrow has occasionally been noted in isolated case reports (1, 14, 19, 20, 38) and Rhoades (39) states that in many of his cases of refractory anemia with hyperplastic marrows exposure to benzene or other myelotoxic agents was recorded. That in chronic benzene poisoning such a combination of a clinical "aplastic" anemia associated with a markedly hyperplastic marrow and even extensive extramedullary hematopoiesis is no coincidence but a characteristic stage of the disease, as Hamilton prophesied, is amply borne out by the cases here reported.

On 14 of the 19 cases reasonably complete postmortem examinations were performed. On 4 cases only a sternal biopsy was obtained and in 1 case our material consisted of a spleen removed at operation and a postmortem biopsy of the tibial marrow. Three additional bone marrow biopsies were obtained on Cases 5, 8 and 14 at intervals of 2 to 13 weeks before death. In each of the autopsied cases histologic material was available from several specimens of bone marrow including both long and flat bones as well as from the usual thoracic and abdominal viscera, including spleen and liver. Lymph nodes were preserved in only 6 cases. The significant positive *gross* and microscopic findings are recorded in the protocols which appear in the appendix. The clinical histories and pertinent laboratory data of the majority of the cases will be found in Dr. Hunter's paper, immediately preceding this one. On the other 8 cases, some of them already published elsewhere *in extensu*, brief clinical abstracts are given. The sex and age of the patients, the nature of their employment, the presumptive duration of contact with benzene and the interval between the last contact and the death of the patient or the time of biopsy are recorded in table 1.

As the series of cases accumulated it became gradually apparent that significant changes were regularly to be found not merely in the bone marrow but throughout the hematopoietic system, including liver, spleen and lymph nodes. No consistent changes were noted in any other organs except frequent purpura of skin, mucous membranes and serous surfaces. The brain was grossly negative in all cases examined except Case 14, which showed several subarachnoid hemorrhages, evidently part of a generalized purpuric process.

No effort has been made to describe in detail the various septic complications of the terminal state. It was consistently noted that pneumonic and other exudates contained relatively few polymorphonuclears, and in a few instances granulocytes were virtually lacking. Hemorrhage was usual in infected foci and necrosis and gangrene were not uncommon.

In the following description of the changes in the hematopoietic system the nomenclature probably deserves a word of comment. In general the terminology of Sabin and her coworkers has been employed (8, 10, 11, 40, 41). In the red cell series erythroblast, normoblast and erythrocyte have been used to signify ascending stages of differentiation. In addition, certain relatively large cells 18 to 30μ

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Bone Marrow

The most marked lesions regularly appeared in the bone marrow. Early in the study of the series it became apparent that the clinical presumption of medullary aplasia was not warranted in the majority of cases. Only six showed severe hypoplasia and in none was there complete aplasia. Three cases exhibited an approximately normal degree of cellularity despite qualitative deviations, three showed definite increase in cellularity, and in five there was marked hyperplasia. Two cases in which a diagnosis of leucemia was made will be discussed separately.

In cases with severe hypoplasia such marked increase in fat was observed that the marrow of the sternum, ribs and vertebrae simulated at first glance marrow from the mid third of the femur of normal individuals. Occasional sinusoids were dilated with erythrocytes and hemosiderin-laden phagocytes but the majority were collapsed and empty. Scattered throughout the tissue, however, were small focal islands of intrasinusoidal hematopoiesis of which two-thirds or more of the component elements were nucleated red blood cells (figs. 1, 2). In one case (Case 14) eosinophilic and neutrophilic granulocytes were present in numbers equal to the erythrogenic cells, but in general granulocytes were few in number and megakaryocytes were rarely encountered. Mitotic figures were likewise infrequent. Despite the generalized hypoplasia a few stem cells, apparently identical with the "megaloblasts" of Peabody, were regularly found. In Case 16, although normoblasts predominated, there were many small clusters of mono- and multinucleated plasma cells. (It is interesting that in this case the blood serum protein was 8 gm. %, and there was a strongly positive formol-gel test; x-rays of the skeleton were negative, there was no Bence-Jones protein in the urine and the patient is still alive.)

With increasing cellularity—to a normal or moderately increased level in the next two groups of cases—a considerable change in the general picture occurred. Several of these marrows showed the development of a fine, fibrillar, eosinophilic substance in and about the sinusoids (fig. 4). The reactions of this substance to the aniline blue connective tissue stain were variable, but frequently a significant amount of the material showed the morphologic and tinctorial properties of collagen and in two cases there was frank fibrosis (fig. 5) with complete replacement of all the marrow fat by dense collagen. This fibrous tissue seemed to replace the fat cells rather

than the hematopoietic elements while the sinusoids appeared to be compressed or obscured by it with resultant distortion and obliteration of the normal architecture.

The increased cellularity of this group of cases was associated with a slight relative decrease in the proportion of normoblasts and a corresponding increase in the number of granulocytes (figs. 3, 4). Myelocytes outnumbered mature polymorphonuclears but never became as numerous as in normal marrow. Megakaryocytes became much more evident and in one case totaled 6% of all the marrow elements. Clasmatocytes also increased considerably and frequently, though by no means always, showed a considerable hemosiderin content. Proportionately the greatest numerical increase occurred in the large basophilic stem cells which occurred in clusters, usually intrasinusoidal, with numerous mitotic figures.

In the final group of marked hyperplasias still further increase in the proportion of these stem cells occurred. In several cases proliferative activity reached extreme proportions, mitotic figures became very numerous and multipolar mitoses not infrequent (fig. 6). Peculiar multinucleated elements unlike any component of normal marrow became very conspicuous. They differed from megakaryocytes in that their nuclei uniformly retained vesicularity, apparent immaturity, and frequently exhibited monstrous proportions. In contrast to the multilobularity of nuclear material ordinarily observed in normal megakaryocytes many of these cells showed either bizarre fusion or no fusion at all of their multiple (2 to 10) nuclei. The appearance of a large proportion of them was indistinguishable from the Sternberg-Reed cell of Hodgkin's disease. The similarity at one extreme to ordinary megakaryocytes and at the other to Sternberg-Reed cells is consistent with the thesis of Medlar (30, 31) that these elements are genetically related. It cannot be denied that in several of these cases the pleomorphic hypercellularity, the multinucleated giant cells, the fibrosis and the numerous mitotic figures simulated deceptively the neoplastic process termed Hodgkin's sarcoma (24). The sole histologic feature restraining such a diagnosis was the unmistakeable interadmixture of erythropoietic elements.

Spleen

As in the case of the bone marrow, the spleen also was always somewhat abnormal and frequently the site of remarkable cellular activity. Although splenomegaly was rarely apparent clinically the organ was often enlarged at autopsy, and in Case 10 it weighed 1800 gm.

Minimal microscopic change (fig. 7), generally associated with hypoplasia of the bone marrow, was evidenced by marked prominence of the sinusoidal littoral cells. These were both larger and more numerous than normal and projected rather deeply into the lumen of the sinusoids. The pulp cords were broadened with an increase in red cell content and a decrease in lymphocytes and polymorphonuclears. Clasmatocytes were increased in number both within the sinusoids and in the pulp and frequently contained phagocytosed red cells or masses of hemosiderin. Even in these cases with

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With progressing severity of the lesion these foci became more numerous and larger, although for the most part they remained intrasinusoidal. The proportion of undifferentiated elements increased and in the masses of stem cells with which the sinusoids were gorged mitotic figures became numerous, multipolar mitoses appeared and atypical multinucleated cells became prominent. The degree and type of differentiation varied considerably from case to case but was always predominantly erythrogenic except in the one case of myeloid leucemia. In most cases, however, a few myeloid elements and varying numbers of fairly normal looking megakaryocytes were seen.

With still further progression of the lesion (figs. 15, 16) the immature cells were no longer confined to the sinusoids but began to invade the pulp and even the periphery of the corpuscles, gradually obscuring the architecture of the organ. In certain, though not all of these marked cases (figs. 9, 17), fibrosis of the pulp became apparent which, as it progressed, still further tended to distort and destroy the usual histologic landmarks. In the most marked instance (Case 10) (fig. 9) this was associated with extreme undifferentiation and exceptionally numerous atypical giant cells (fig. 8) and multipolar mitoses which, as in the similar bone marrow picture already described, closely simulated so-called Hodgkin's sarcoma.

A general, though by no means exact parallelism could be traced between bone marrow and splenic hematopoietic activity. Case 4, however, showed maximal hyperplasia of the marrow and *only* traces of splenic erythropoiesis, whereas in case 8 the most marked splenic erythropoiesis observed in the series (in fact far beyond any that the authors have ever observed) was associated with distinctly diminished marrow cellularity. Fibrosis occurred sporadically in both spleen and bone marrow without definite relationship. It was marked in the marrow in Case 8 but scanty in the spleen. It reached a maximal grade in the spleen in Case 10, whereas the marrow showed very little. In the spleen significant fibrosis was found only in association with very active and atypical hematopoiesis, whereas in the marrow it was associated with varying grades of cellularity but not with either extreme aplasia or extreme hyperplasia.

In cases with minimal splenic changes the Malpighian corpuscles were ordinarily small but intact. With advance of the process they tended to become obscured, in part by intrinsic degeneration and subsequent fibrosis (fig. 17), in part by perifollicular hemorrhage and in some instances by invasion of proliferating elements from the surrounding pulp. These invading cells sometimes formed a wide collar about the follicle and tended to obscure its delimitation from the surrounding pulp. No frank lymphoid hyperplasia was observed though in some of the severe cases a high proportion of the persisting cells in the shrunken and deformed corpuscles were lymphoblasts.

The greatly enlarged spleen removed surgically from Case 19 was markedly hematopoietic and differed in no essen-

tial way from the postmortem organs of other caaes.

LIVER

Changes in the liver were much leas striking than those noted in either the spleen or bone marrow. Kupffer cells were invariably prominent and usually loaded with hemosiderin. Central necrosis of varying extent was frequently present .but always appeared to be of short duration, judging from the acuteness of the reaction, and probably did not often much antedate the agonal state. It would seem more reasonable to correlate it with the terminal infection so generally present than with any direct effect of benzene upon the liver. It showed little correlation with icterus, being absent in frankly jaundiced patients and present in patients showing no trace of icterus.

In the majority of cases showing marked erythropoiesis in either bone marrow or spleen small foci of intrasinusoidal erythroblasts and normoblasts appeared. In Case 10 relatively large numbers of stem cells were present and few normoblasts were observed. As in the other organs of this patient a marked tendency to giant cell formation was apparent (fig. 18).

LYMPH NODES

Lymph nodes were only occasionally noted to be grossly enlarged but frequently were prominent at autopsy because of a dusky pinkish hue which made them stand out prominently from the surrounding fatty tissue. Sections were available for study in only 6 cases but the findings varied considerably. Minimal changes consisted of marked dilatation of the sinuses and concomitant diminution in the lymphoid pulp. The sinuses were frequently packed with active clasmatocytes (fig. 10) to give the picture which has been termed "sinus catarrh" (17). In 2 cases interlacing cords of these cells packed the sinuses, and in the interstices large numbers of erythrocytes and free clasmatocytes were seen. There was active phagocytosis of red cells both in the sinuses and in the remaining nodal parenchyma.

Lymphoid cords showed slight to almost complete loss of lymphocytic content associated with a marked grade of edema and loss of follicular identity. In several nodes there was focal evidence of partial lymphoid regeneration accompanied by the appearance of pale staining elements identified as stem cells and lymphoblasts. Few of these immature cells appeared in the sinuses, the majority being confined to the pulp. Metaplastic transformation to myeloid elements was occasionally evident, myelocytes, normoblasts, and even megakaryocytes being noted in regenerating lymphoid cords. Accompanying apparent increase in parenchymatous substance there was an increase of stromal fibrous tissue and compression of previously dilated sinuses.

Lymph nodes were unfortunately not available in the cases demonstrating the most advanced lesions in the spleen and bone marrow. Through the kindness of Dr. Ellis Kellert of the Ellis Hospital Laboratory, Schenectady, New York, however, the authors have been privileged to examine a section of lymph node from another case of chronic benzene poi-

soning in which the appearanc liver, spleen and bone marr exactly similar to that noted Case 10, which resembled H disease. In this lymph node chymatous regeneration and plasia were sufficiently exces compress the sinuses and obsc architecture (fig. 11). The nc tained a loose fibrous stron intermingled lymphocytes, 1 blasts, stem cells, normobla multinucleated giant cells (f none of which showed extre dominance.

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soning in which the appearance of the liver, spleen and bone marrow was exactly *similar* to that noted in our Case 10, which resembled Hodgkin's disease. In this lymph node parenchymatous regeneration and metaplasia were sufficiently excessive to compress the sinuses and obscure the architecture (fig. 11). The node contained a loose fibrous stroma with intermingled lymphocytes, lymphoblasts, stem cells, normoblasts and multinucleated giant cells (fig. 19), none of which showed extreme predominance.

The Leucemias

Two cases in this series are so different from the rest that their description has been reserved for a separate paragraph. Case 15 (FTH-#87) as may be learned by reference to Dr. Hunter's paper, had been exposed to benzene for 10 years, 4 years heavily and the succeeding 6 years lightly, and had from the start of his employment shown hematologic evidence of benzene intoxication. In the last 3 months of his life he developed the typical picture of an acute myeloid leucemia. At autopsy the characteristic findings of leucemia were manifest with diffuse myeloid infiltration of the liver, spleen and bone marrow. An unusual manifestation was a localized tumor nodule, 4 cm! in diameter, in the liver which on microscopic examination proved to be a true leucemic tumor (figs. 12, 13) composed of undifferentiated myeloid cells, stem cells and atypical multinucleated cells which invaded, disrupted and had replaced the liver substance. It was also thought that the bone marrow showed rather more persistent erythrogenic tissue than would be expected in a leucemia of this type.

The second case was a boy of twelve, a painter's son, who played frequently in his father's shop and had amused himself by frequently repainting his toys in different colors using a paint remover known to contain benzene to remove the preceding coat of paint. He developed a clinical picture of aplastic anemia but sternal puncture in one hospital and sternal biopsy in another, which we were privileged to examine through the courtesy of Dr. Earle Chapman, revealed a typical leucemic replacement of the marrow with very undifferentiated cells of the lymphoblastic series. No features suggestive of a benzene reaction on the part of the erythrogenic series could be made out.

Discussion

Since all but three of the cases included in this report were fatal—and a speedy demise is to be expected in one of the remainder if our diagnosis of acute aleucemic leucemia is correct—it is evident that the earlier phases of benzene poisoning are not exemplified. None of the cases had less than 6 months' contact with the fumes and only 4 cases had leas than a year's *exposure.* Eight were subjected to contact from 1 to 4 years and the remaining seven for 4 to 12 years. Nevertheless a wide variation in tissue response has been recorded. Excluding for the time being the two leucemias, one can divide the remaining cases into two groups—six cases with marrows less cellular than normal (Cases 1, 3, 6, 11, 14 and 16) and nine with frank hyperplasia (2, 4, 5, 7, 9, 10, 12, 13, and 18). Two cases are

difficult to classify and appear to occupy a somewhat intermediate position: Case 17 because the cellularity was within normal limits though a slight shift to the left in degree of differentiation suggests a hyperplastic tendency, and Case 8 with a definitely hypoplastic marrow but the most active and extensive extramedullary hematopoiesis of the series.

Benzene, therefore, is a toxin which under varying conditions can produce diverse reactions in exposed individuals. Is it possible to determine any of the factors responsible for this diversity?

Biologically toxic agents can be roughly classified into two categories: substances which with adequate *exhibition* will produce their effects upon all individuals exposed, and a second group which in minute dosage will produce devastating effects upon occasional individuals that cannot be duplicated in the majority of apparently similar beings by an exaggeration of the dosage. To which category benzene belongs is still uncertain. Possibly adequate exposure would affect all individuals but clinical experience strongly suggests that the effect of minimal dosage is extremely variable and that individual idiosyncrasy is of great importance. Animal experimentation in various investigators' hands has confirmed the variability of host reaction even under uniform controlled conditions but has given us no explanation of the mechanism. Clinical investigation has yet to scratch the surface of the problem. Dosage—both intensity and duration of exposure—must be estimated with far greater accuracy in *many* more individuals than has heretofore been possible before an assessment of its importance in comparison with variability of host reaction can be made. Nevertheless, inadequate as our data are, they do permit an attempt to analyze some of these factors and suggest some tentative conclusions which are of interest.

Among the factors which might influence the reaction of the marrow, intensity of exposure must be considered. By analogy with other *toxins* it seems reasonable to suppose, if intensity is of importance, a high degree would produce an overwhelming aplastic result, a lower intensity a stimulating hyperplastic one. Unfortunately, the available data are scant. Case 17 (FTH-#81), a telephone operator, was in the habit of cleaning off paint marks from the switchboard with a paint remover shown to contain approximately 50% benzene. Since the process did not take more than ½ to 1 hour per day, the degree of daily exposure cannot have been great. Nevertheleas she showed a marked hypoplasia at autopsy. Cases 7, 8 and 16 were workers in the same factory. Case 7 worked for 12 years before illness compelled him to give up his position. Case 8 took over his job but was able to hold it only 1½ years before weakness compelled him also to give up. Case 16 assisted Case 8 and worked over the same vat with him. Intensity of exposure must have been approximately equal in these three workers, yet Case 7 showed at autopsy marked medullary hyperplasia, Case 8 an aplastic marrow but a hematopoietic splenic tumor, while case 16 (still living) showed on sternal biopsy a definitely diminished cellularity. So far as our evidence goes it does not

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3		F	20	Rubl
4		M	25	Artif
5		M	46	Cobt
6		F	44	Rubl
7	1	M	48	Artif
8	2	M	45	Artif
9	32	M	45	Artif
10	34	M	43	Artif
11	35	F	18	Rubt
12	79	M	54	Artif
13	80	M	51	Cobb
14	81	F	63	Telep
15	87	M	28	Artif
16	88	M	57	Artif
17	10	M	57	Artif
18		M	41	Furn
19		M	12	Scho

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suggest that intensity of exposure is the determining factor in the bone marrow reaction.

Duration of exposure, however, does seem to be of importance. Checking the lists of the two types of cases against table 1 it is apparent that the 3 cases with fatal outcome within less than 1 year of initial exposure showed depression of marrow activity and that no case with a hyperplastic marrow had been exposed for less than 2 years. The converse does not, however, hold true, for 2 cases with prolonged exposure (6 and 14) showed aplastic marrows. Case 8 with 1½ years' exposure appears to occupy a middle ground between the two series with its definitely hypoplastic bone marrow and its active extramedullary hematopoiesis.

Since all the cases with less than a year's exposure showed hypoplasia and most of the cases with prolonged exposure hyperplasia, one is tempted to conclude that the initial effect of benzene on the bone marrow is to depress it, whereas the later effect is to stimulate it. This may or may not be true, but no such conclusion is warranted by the data at our disposal. An equally tenable hypothesis would be that benzene may cause either hyperplasia or aplasia, the former enabling the patient to carry on for many years despite continued exposure, the latter leading to a prompt fatality if the patient is not quickly

TABLE 1

CASE	FTH #	SEX	AGE	INDUSTRY	DURATION OF CONTACT	INTERVAL SINCE LAST CONTACT
1		M	22	Rubber factory	6 months	9 months (N)
2		M	54	Artificial leather	7 years	1 month (N)
3		F	20	Rubber cement	8 months	1 month (N)
4		M	25	Artificial leather	3 years	1 month (N)
5		M	46	Cobbler'	years	1 month (N)
6		F	44	Rubber factory	4 years	6 months (N)
7	1	M	48	Artificial leather	12 years	5 months (B)
8	2	M	45	Artificial leather	1½ years	4 months (N)
9	32	M	45	Artificial leather	3 years	1½ years (N)
10	34	M	43	Artificial leather	years	? (N)
11	35	F	18	Rubber factory	7 months	1 month (N)
12	79	M	54	Artificial leather	3 years	3 months (N)
13	80	M	51	Cobbler.	2 years	? (N)
14	81	F	63	Telephone operator**	5 years	3 months (N)
15	87	M	28	Artificial leather	4 years	6 years (N)
16	88	M	57	Artificial leather	1 year	2 years (A) (B)
17	10	M	57	Artificial leather	5 years	5 months (A) (B)
18		M	41	Furniture finisher***	years	2) months (N)
19		M	12	Schoolboy***	?	2 months (A) (B)

(N) Necropsy, (B) Biopsy, (A) Alive.
Case number in Dr. Hunter's series.
* Used benzene as solvent for rubber cement.
** Used solvent containing 50% benzene for eradicating names on switchboard.
*** Used paint remover containing benzene.

removed from contact. The experiments of Schilowa (44) may be cited in partial confirmation of such a hypothesis. In several series of dogs identical dosage produced hyperplastic changes in some, aplasia in others and no effect in still other animals.

Since the peripheral blood often reflects imperfectly or, in our present state of knowledge, even misleadingly the state of the bone marrow, the actual progression of medullary changes can only be determined by repeated marrow punctures or biopsies. Our own material is insufficient to warrant any conclusions. Biopsy was performed on Case 5 eight weeks before death, on Case 8 two weeks antemortem and on Case 14 thirteen weeks and again 5 weeks before exitus. Case 5 belongs to the hyperplastic group, Case 14 to the aplastic and Case 8 was the intermediate one. In none of the three cases was there a significant difference between the biopsy specimen and the subsequent autopsy findings. Finally, in the two surviving cases, cases which despite fairly prolonged exposure may be considered to be at a relatively early stage of the disease since their apparent cure indicates that the process was still reversible, Case 16 showed well marked hypoplasia and Case 17 slight hyperplasia.

Another matter worthy of analysis is the relationship between the state of the marrow and the interval since the last contact with bensene. Eight cases died within 3 months of their last exposure, and of these, five showed hyperplasia and three relative aplasia. At the other extreme, five cases had had no contact with the agent for periods varying from 6 months to 2 years. Two of these fall in the hyperplastic and three in the aplastic group. The interval since exposure may therefore be eliminated as the determining cause of the varying bone marrow pictures.

Correlation with age and sex reveals somewhat more interesting results. Eliminating as before from our figures the leucemias and the indeterminate Case 8, we find 4 patients below the age of 30 and twelve above it. Of the former, three showed aplasia and only one hyperplasia; in the older group in contrast nine showed hyperplasia and only three aplasia. Surprising, at first glance, with their suggestion that the older marrows are more capable of a proliferative reaction than the younger ones, these figures do not stand analysis. Only one of the individuals below thirty had been exposed for more than a few months, whereas all of the group above thirty had had from 1 to many years of exposure.

In relation to sex, the figures, though too few to be conclusive, are distinctly more suggestive. Taking the same group of 16 cases we find 12 males and 4 females. Ten of the males showed hyperplasia and only two aplasia. All four females showed aplasia. Among the males the only two showing aplasia had exposures of 6 months and 1 year respectively. Among the 4 females are the only two cases in the entire series with aplastic marrows in the face of prolonged (4 and 5 years) exposure. The number of females is, of course, too small to justify wide generalization. That females also can react to prolonged exposure to benzene with extreme and atypical hyperplasia

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is shown by the case of Kellert already cited. A tendency, however, of the male to react with hyperplasia, of the female with aplasia is suggested and may help to explain, since the hyperplastic form of the disease has not yet won general recognition, the prevailing opinion that females are more susceptible.

No discussion of the anemias of benzene poisoning can be terminated without mention of the close similarity of many of these hyperplastic marrows, composed predominantly of immature erythrogenic elements, to the bone marrows described by Martland (29-a) in chronic radium poisoning. A still more surprising, though probably accidental parallelism exists in the prolonged latency between exposure and the development of symptoms or detectable signs frequently observed in the two conditions. The authors can do no more than express their amazement that a simple, volatile organic chemical, readily eliminated via the respiratory tract can initiate a train of pathologic sequences which can progress for months and even years after exposure has ceased.

A still more controversial field is entered in considering the relationship of chronic exposure to benzene to the development of leucemia or other neoplastic conditions. Penati and Vigliani (37) in a recent review of the literature were able to collect 10 cases of leucemia in patients who had verified histories of exposure. Virtually all varieties of the leucemic state have been recorded: chronic myeloid (52), chronic lymphatic (14), acute leucemia (9), acute aleucemic leucemia (49). To these we have added a case of acute myeloid leucemia (Case 15) and another of acute aleucemic leucemia (Case 19). It is interesting to note, since the issue of sex has already arisen in relation to the hyperplastic anemias, that 8 of the 10 patients cited by Penati and Vigliani were males, and our 2 cases were of the same sex.

Twelve cases of leucemia developing among the unknown thousands exposed to a solvent so widely used throughout the industrial world (33, 43) do not constitute in themselves an impressive figure. They gain in significance, however, when viewed in the light of certain other observations. Most important is the experimental work of Lignac (27, 28). Working with a strain of mice ordinarily free from diseases of the hematopoietic system, he observed the development of leucemia and malignant lymphoma in 8 of 33 animals following minute repeated doses of benzene over a long period of time. This observation still lacks independent confirmation.

Also suggestive to anyone who has studied even superficially cases of the hyperplastic type which have been presented in this article are the evidences of what, for want of a better term, may be called a neoplastic tendency. The degree of anaplasia, the rapidity of growth as judged by the number of mitotic figures, the development of cells having no counterpart in normal tissues but common to a variety of malignant tumors are phenomena characteristic of neoplasia which the authors have never heretofore met in such marked degree in non-neoplastic states. Certainly no more favorable conditions

for the development of neoplasm can be imagined than prolonged and intense stimulation of reproductive activity and simultaneous arrest of maturation.

The evidence that chronic exposure to benzene produces leucemia in human beings is still incomplete but it is accumulating at a rate and to a volume which command serious consideration.

PROTOCOLS*

Case 1. F. W. A., *22,* male. A *22* year old American laborer entered the hospital complaining of purpura.

Three years ago the patient worked in a rubber factory for a period of several months. Following this he suffered intermittently from headache, dizzy spells and occasional epistaxis. One year ago, while at sea, he suddenly became quite weak and pallor was noted. He returned ashore, rested for 3 months, and 9 months prior to admission he again returned to work in a rubber factory, where he was exposed to benzene fumes. After 6 months of this work he began to suffer from throbbing headaches, palpitation and profound weakness. He stopped work but the symptoms continued and he developed dyspnea and migratory joint pains. For about 2 weeks there was constant oozing nosebleed, the stools became tarry, the gums bled readily and multiple black and blue marks appeared on the skin. These features were evident on examination at entry. There was very marked pallor. Lymph nodes, liver and spleen were not felt.

Laboratory Findings: The red blood count was 1,200,000, with 30% hemoglobin. The white cells numbered 2,600, with 39% polymorphonuclears, 50% lymphocytes, 9% monocytes, 1% eosinophils and 1% basophils. There were no immature cells or nucleated red cells. Reticulocytes numbered 0.9% and the platelets 46,000 per cu. mm. The bleeding time was 36 minutes, the clotting time 38 minutes. Fragility of red cells was normal. There was no clot retraction in 48 hours.

The patient was given five transfusions but bleeding from the mucous membranes became profuse. The red cell count fell to 600,000 and the patient died on the 39th hospital day.

Necropsy: Skin: Marked pallor, scattered small purpuric spots.

Serous Cavities: Petechial hemorrhages of pericardium.

Lungs: Marked edema and congestion.

Liver: 1415 gm. Kupffer cells markedly increased in prominence and filled with hemosiderin. Portal islets negative except for slight hemosiderosis. Central lobular necrosis moderate with polymorphonuclear exudate.

Spleen: 70 gm. Corpuscles are present in normal numbers but are quite small and misshapen. Content normal. Architecture is preserved and there is minimal hemosiderosis. Splenic cords are widened and show slight fibrosis. Littoral cells are unusually prominent and project into sinusoids. Sinusoids contain scattered stem cells, normoblasts and rare myelocytes.

Bone Marrow: Architecture preserved, with marked increase in fat and minimal cellularity. Fibrosis is absent and hemosiderosis slight. Sinusoids are collapsed but there are small intrasinusoidal foci of hematopoiesis in which normoblasts predominate.

Case 2. W. D. S., 54, male (5).

A 54-year-old factory worker entered complaining of bleeding from the gums.

For 7 years the patient had operated a spreading machine in an artificial leather factory, in the process of which he was constantly exposed to benzene fumes. About a year before entry he first noted occasional bleeding from the gums and a slightly productive cough. For about 2 months there was slight swelling of the ankles and puffiness of the eyelids associated with polyuria and polydipsia. For 6 weeks there was constant bloody oozing from the gums. Examination on admission showed pallor, marked hemorrhagic oozing from the gums and numerous purpuric spots on the skin.

* Cases included in the clinical studies by Dr. F. T. Hunter are denoted by the parenthetic expression (FTH #).

The tip of the spleen was barely and the liver edge extended 6 cm. the costal margin.

Laboratory Findings: Urine wa tive. Red blood count was 1,900,0 45% hemoglobin. The white cel bered 2,800, with 16% polymorphor 52% lymphocytes, 8% monocytes, 4 ophils and 14% basophils. The marked stippling of red cells, oc nucleated red cells and rare myel Platelets were markedly reduced bers. Reticulocytes were 2%. time was over 20 minutes and there clot retraction in 48 hours. The index was 8 units.

The patient was given five tran without improvement. He died on hospital day.

Necropsy: Skin: Icteric, multi techial hemorrhages. Edema bot extremities.

Lungs: Pulmonary edema and rhagic bronchopneumonia with re cells and fibrin but relatively fe morphonuclears.

Liver: 2095 gm. Kupffer cells m prominent and filled with hemc Islets negative. Within the sinus scattered immature blood cells and ate numbers of clasmatocytes.

Spleen: 480 *gm.* Corpuscles in numbers but compressed by surr collars consisting of dense aggrega indeterminate stem cells accompai a few normoblasts and phagocytes. cords are widened and contain hemc extravasation and hemosideri phagocytes. Lining cells of sinus prominent. Many of the sinusoi filled with stem cells, erythroblas occasional normoblasts. There a some clssmatocytes with both red an cells ingested. Architecture is g preserved save for a few foci in which of stem cells obscure the structure.

Bone Marrow: Markedly increase larity in both rib and femoral marro fat remains and there is no evid fibrosis. Architecture is oblitera large clusters of stem cells, eryth and normoblasts, although moderat bers of myelocytes and polymorphor may also be observed. Megakar

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The tip of the spleen was barely palpable and the liver *edge* extended 6 cm. beneath the costal margin.

Laboratory Findings: Urine was negative. Red blood count was 1,900,000, with 45% hemoglobin. The white cells numbered 2,800, with 16% polymorphonuclears, 52% lymphocytes, 8% monocytes, 4% eosinophils and 14% basophils. There were marked stippling of red cells, occasional nucleated red cells and rare myeloblasts. Platelets mere markedly reduced in numbers. Reticulocytes were 2%. Bleeding time was over 20 minutes and there was no clot retraction in 48 hours. The icterus index was 8 units.

The patient was given five transfusions without improvement. He died on the 28th hospital day.

Necropsy: Skin: Icteric, multiple petechial hemorrhages. Edema both lower extremities.

Lungs: Pulmonary edema and hemorrhagic bronchopneumonia with red blood cells and fibrin but relatively few polymorphonuclears.

Liver: 2095 gm. Kupffer cells markedly prominent and filled with hemosiderin. Islets negative. Within the sinusoids are scattered immature blood cells and moderate numbers of clasmatocytes.

Spleen: 480 gm. Corpuscles in normal numbers but compressed by surrounding collars consisting of dense aggregations of indeterminate stem cells accompanied by a few normoblasts and phagocytes. Splenic cords are widened and contain hemorrhagic extravasation and hemosiderin-laden phagocytes. Lining cells of sinusoids are prominent. Many of the sinusoids are filled with stem cells, erythroblasts, and occasional normoblasts. There are, also some clasmatocytes with both red and white cells ingested. Architecture is generally preserved save for a few foci in which masses of stem cells obscure the structure.

Bone Marrow: Markedly increased cellularity in both rib and femoral marrow. No fat remains and there is no evidence of fibrosis. Architecture is obliterated by large clustera of stem cells, erythroblasts and normoblasts, although moderate numbers of myelocytes and polymorphonuclears may also be observed. Megakaryocytes are rare, mitotic figures abundant, and occasional giant cells with monstrous nuclei may be seen. Phagocytes with hemosiderin are abundant.

Case 8. E. M., 20, female (23, 4; 6). A 20-year-old Canadian shoe factory worker entered the hospital complaining of nosebleed.

Eight months before entry the patient began to work at applying rubber heels. The cement solvent which she used in her daily work showed on analysis a content of 80% benzene. After 4 months she noted nausea and easy fatigability which progressed rapidly during the ensuing month. Two months before entry purpuric phenomena appeared. There was first epistaxis, next menorrhagia, and finally bleeding from the *gums.* Uncontrollable epistaxis brought her to the hospital, where examination showed pallor, a foul breath, Vincent's infection of the gums, and purpuric spots on the skin.

Laboratory Findings: Red blood count 1,715,000, with 40% hemoglobin. The white cells numbered 1,200, with 16% polymorphonuclears, 76% lymphocytes and 8% monocytes. Platelets were greatly diminished and no reticulocytes were seen. The bleeding time was 16 minutes and the clotting time 12 to 19 minutes.

Despite 12 transfusions in 19 days the course was progressively downward. The patient developed otitis media and bronchopneumonia and death followed profuse pulmonary and vaginal hemorrhages.

Necropsy: skin and Sclerae: Icteric. Petechial hemorrhages of serous cavities and mucous membranes of stomach and bladder.

Lungs: Show large foci of hemorrhagic pneumonia without polymorphonuclear reaction.

Liver: 1220 gm. Kupffer cells moderately prominent, minimal hemosiderin content. Islets and sinusoids are negative. Parenchymatous cords show slight central fraying.

Spleen: 125 gm. The corpuscles are normal in number but are unusually small and are surrounded by broad hemorrhagic collars containing moderate numbers of phagocytes. Architecture is preserved but

sinusoids are small. Littoral cells prominent. There is no hematopoiesis. Pulp cords are broad, hemorrhagic and contain scattered lymphocytes, plasma cells and monocytes. There is a small amount of hemosiderin.

Lymph Nodes: Slightly enlarged and considerably redder than normal. No sections available.

Bone Marrow: Femoral marrow is totally fatty with minimal evidence of hematopoiesis. Marrow elsewhere is mostly fatty and sinusoids are collapsed. There are scattered small clusters of intrasinusoidal normoblasts and occasional phagocytes.

Case 4. N. A., *25,* male. A 25-year-old Greek factory hand entered the hospital complaining of fever and weakness.

For 3 years the patient had worked in a leather factory using a spray containing benzene. Eleven days before entry he developed chills, fever and a severe headache. During the week preceding entry there was frequent vomiting of blood-streaked material which gradually became coffee ground in character. There was a hacking cough, and 2 days before entry jaundice and herpes labialis appeared. Examination showed the patient to be pallid but deeply icteric. The liver and spleen were not felt.

Laboratory Findings: The red blood count was 3,300,000, with 70% hemoglobin. The white cells numbered 3,800, with 1% polymorphonuclears, 98% lymphocytes and 1% myelocytes. Platelets were markedly reduced and an occasional nucleated red cell waa seen. Red cell fragility was normal and the clotting time was 9 minutes. The van den Bergh showed 13.5 mg.% of bilirubin and a liver function test (bromsulphalein) showed 85% retention of dye at the end of 1 hour.

(The white cell count was reported as being 16,000 and 12,000 four and three days respectively before entry. Almost all of the cells were lymphocytes.)

The patient was given 5 transfusions without benefit and died on the 14th hospital day.

Necropsy: Skin: Pallid and markedly icteric.

Liver: Considerable increase in periportal fibrosis with infiltration by lymphocytes. Proliferation of bile ducts but no evidence of necrosis. Scant normoblastic hematopoiesis in sinusoids.

Spleen: Corpuscles are small and diminished in number. Architecture is preserved but splenic cords are widened, hemorrhagic and contain large deposits of hemosiderin. Sinusoids show prominence of the littoral cells, rare clusters of normoblasts and an occasional megakaryocyte.

Lymph Nodes: Architecture preserved but there are no follicles or germinal centers. Cords are negative. Sinuses are markedly dilated and filled with strands of phagocytic cells intermingled with which are large numbers of red blood cells and free clasmatocytes filled with debris, erythrocytes and polymorphonuclears.

Bone *Marrow:* There is a maximal cellularity with no fat present. Predominant cells, 95% of elements present, are normoblasts. Granulocytes and stem cells are minimal but there are moderate numbers of megakaryocytes. Phagocytic cells and hemosiderin are sparse.

Case 6. L. C., 46, male (6a). A 46-year-old Italian cobbler entered the hospital complaining of headache and dizzy spells.

For 7 years the patient had cemented leather soles with a rubber cement believed to contain benzene. Five months before entry he began to tire easily. Two months later he had palpitation with the slightest exertion and headaches. He noted thereafter increasing pallor, frequent epistaxis, and bleeding from the gums. Examination showed pallor, and purpura of the skin and mucous membranes. There were systolic and faint diastolic murmurs over the base of the heart. The liver and spleen were not felt.

Laboratory Findings: The red cell count was 1,050,000, with 30% hemoglobin. The white cells numbered 1,400, with 36% polymorphonuclears, 49% lymphocytes, 2% monocytes, 3% myelocytes, 8% myeloblasts, and 2% unclassified cells. Platelets were very few in number.

A sternal biopsy done 8 weeks before death was inadequate in amount but showed hyperplasia and a shift to the left in both the red and white cell series. Nucleotide therapy for 30 days produced no im-

provement. The patient grew pro worse, the stools became tarry, a of the left buttock developed an suddenly 10 weeks after admissi episode suggestive of pulmonary e

Necropsy: Skin: Few scattered spots.

Lungs: Acute pleuritis on right cc. fluid. Right lung almost co consolidated by hemorrhagic pneumonia with exudate consisting serous fluid, red cells, phagocy relatively few polymorphonucles two small acute infarcts.

Inferior Vena Cava: Adherent thrombus extending from right iliac vein.

Liver: 1700 gm. Central thre of all lobules shorn marked fra disintegration of cell cords. M increased prominence of Kupffer engulfed hemosiderin. Islets Rare small clusters of normo sinusoids.

Spleen: 50 gm. Architecture and corpuscles normal in numb slightly compressed. Cords are ately broadened and contain small of lymphocytes, monocytes, and patchy fibrosis. There is con hemosiderosis. Sinusoids contain ate numbers of phagocytes and of early hematopoiesis in which nor predominate although small nux myelocytes are also present.

Lymph Nodes: Slightly enlarged, pink. Follicles are barely evide minal centers are absent. Archit preserved. Sinuses filled with ph as in Case 4. Cords are various atous with infiltrating monocytes o foci of plasma cells, myelocytes an hlaats. There are occasional me cytes and moderate numbers of figures.

Bone *Marrow:* Vertebrae, ribs a num show no fat and a barely evide ground of thin fibrous stroma. Ce is increased numerically over the content. There are many large of stem cells although two-third marrow content consists of nom Mitotic figures are abundant and t moderate numbers of myelocytes,

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provement. The patient grew progressively worse, the stools became tarry, an abscess of the left buttock developed end he died suddenly 10 weeks after admission in an episode suggestive of pulmonary embolism.

Necropsy: Skin: Few scattered purpuric spots.

Lungs: Acute pleuritis on right with 500 cc. fluid. Right lung almost completely consolidated by hemorrhagic bronchopneumonia with exudate consisting of fibrin, serous fluid, red cells, phagocytes, and relatively few polymorphonuclears. Also two small acute infarcts.

Inferior Vena Cava: Adherent granular thrombus extending from right internal iliac vein.

Liver: 1700 gm. Central three-fourth of all lobules show marked fraying and disintegration of cell cords. Moderately increased prominence of Kupffer cells with engulfed hemosiderin. Islets negative. Rare small clusters of normoblasts in sinusoids.

Spleen: 50 gm. Architecture preserved and corpuscles normal in numbers but slightly compressed. Cords are moderately broadened and contain small numbera of lymphocytes, monocytes, and minimal patchy fibrosis. There is considerable hemosiderosis. Sinusoids contain moderate numbers of phagocytes and evidence of early hematopoiesis in which normoblasts predominate although small numbera of myelocytes are also present.

Lymph *Nodes:* Slightly enlarged, soft and pink. Follicles are barely evident; germinal centers are absent. Architecture is preserved. Sinuses filled with phagocytes as in Case 4. Cords are variously edematous with infiltrating monocytes orcontain foci of plasma cells, myelocytes and normoblasts. There are occasional megakaryocytea and moderate numbers of mitotic figures.

Bone Marrow: Vertebrae, ribs and sternum show no fat and a barely evident background of thin fibrous stroma. Cellularity is increased numerically over the normal content. There are many large clusters of stem cells although two-thirds of the marrow content consists of normoblasts. Mitotic figures are abundant and there are moderate numbers of myelocytes, mature granulocytes, and but a few megakaryocytes and phagocytes. The femoral and tibial marrows show evidence of fat resorption with increased cellularity qualitatively similar to that in the vertebrae but quantitatively not quite as abundant.

Case 6. M. McK., 44, female (6b). A 44-year-old Canadian factory worker entered the hospital complaining of weakness and headache.

For 4 years, until 3 months before admission, the patient had been employed in a rubber factory and had been exposed to benzene fumes. Three years before entry she had noted soreness of the gums and tongue. One and a half years later there waa numbness of the hands and toes. For 8 months there had been dyspnea on exertion. Seven weeks before entry a hemorrhoidectomy was performed and at that time her physician noted that she had anemia. Examination showed pallor and retinal hemorrhages. Vibratory sense was impaired. The liver and spleen were not palpable.

Laboratory Findings: The red blood count was 1,150,000, with 40% hemoglobin. The white cells numbered 1,200, with 28% polymorphonuclears, 32% lymphocytes, 28% myelocytes, 4% myeloblasts and 8% monocytes. Platelets were greatly reduced. The bleeding time was 30 minutes.

Repeated transfusions (40) produced only transient improvement. Purpuric manifestations became progressively more severe and she passed blood copiously in the urine, stools and per vaginam. She died 5 months after entry with symptoms suggesting peritonitis.

Necropsy: Skin: Bloated by marked accumulation of subcutaneous gas. Terminal gaa bacillus septicemia.

Cecum: Severe acute and chronic typhilitis with ulceration, probably the portal of entry for the terminal infection.

Liver: 1600 gm. Contains bubbles of gas. Extensive marked postmortem degeneration of hepatic cords. Islets negative. Hemosiderin in Kupffer cells is markedly increased in amount. Sinusoids contain rare small clusters of normoblasts.

Spleen: 125 gm. Corpuscles normal and architecture preserved. Pulp cords show marked hemosiderosis and moderate fibro-

sis. Sinusoids show prominent littoral cella with abundant phagocytosis of hemosiderin and contain a few small clusters of normoblasts.

Bone Marrow: Vertebral and femoral marrow fatty. Sinusoids are dilated and filled with erythrocytes and thin fibrous strands. There are scattered and occasionally clustered normoblasts and .moderate numbers of hemosiderin-laden phagocytes.

Case 7. E. G. T., 48, male. (FTH #1)

Biopsy: Bone *Marrow:* There is no fat or fibrosis. Marrow is intensely cellular with erythrogenic activity predominating. White cell elements are greatly diminished and there are relatively few mature cella. There are large clusters and fused nodules of normoblasts and stem cella with abundant mitotic figures. Very slight hemosiderosis is apparent.

Case 8. L. M., 46, male (16). (FTH 12)

Necropsy: Marked pallor of skin and mucous membranes. Many purpuric spots measuring up to 6 cm. Large amount of tarry material in intestinal tract.

Liver: 2,000 gm. Central lobular necrosis with scant polymorphonuclear and marked monocytic reaction. Kupffer cells very prominent and filled with hemosiderin as in Case 1. Islets negative. In the sinusoids are small numbers of scattered and clustered stem cells and normoblasts. Rare megaksryocyte seen.

Spleen: Architecture preserved but corpuscles few and obviously compressed. Pulp cords thin and contain few cells but much hemosiderin. Sinusoids are enormously distended with large numbers of stem cells, erythroblasts and normoblasts. There are numerous mitotic figures, frequently multipolar in character, and moderate numbers of multinucleated giant cells resembling megakaryocytes. Only a rare granulocytic element is seen.

Bone *Marrow:* Architecture obliterated by dense fibrosis without evidence of fat or sinusoids. There are large deposita of hemosiderin and numerous clasmatocytes. Cellularity is slightly less than normal and irregular in distribution—some areas are densely cellular and others relatively sparsely cellular. Predominant elements are normoblasts, erythroblasts and stem cells frequently forming large nodular clusters. Granulopoiesis is scant and there are very few true megakaryocytes present.

Case 9. P. F. M., 47, male. (FTH 132)

Necropsy: Skin: Pallid; multiple crusted hemorrhagic and occasionally purulent lesions on extremities. Multiple petechial hemorrhages and decubitus ulcers.

Lungs: Focal abscess formation with necrosis.

Pericardium: 50 cc. of hemorrhagic fluid.

Liver: 2,000 gm. Kupffer cells very prominent and filled with hemosiderin. Scattered immature blood cells in the sinusoids.

Spleen: 200 gm. Architecture preserved, corpuscles present but diminished in number. Pulp cords thin and hemorrhagic. Sinusoids filled with moderate numbers of stem cells, erythroblasts, plasma cells, normoblasts and clasmatocytes. There are occasional granulocytes and rare megakaryocytes.

Bone *Marrow:* Fat considerably diminished and replaced by marrow cells. Latter exceed the normal in number and are predominantly erythrogenic, consisting of normoblasts, erythroblasts and stem cells, frequently in clusters. Megakaryocytes and granulocytes considerably diminished in numbers. Hemosiderosis, slight.

Case 10. F. B., 43, male. (FTH #34)

Necropsy: Liver: Extensive early central necrosis. The Kupffer cells contain moderate amounts of hemosiderin. Islets contain small foci of hematopoiesis, usually erythrogenic but occasionally granulocytogenic. Sinusoids contain many discrete cells and occasional clusters of normoblasts, large stem cells, and giant multinucleated cells with bizarre irregular nuclei and abundant basophilic cytoplasm. There are many unipolar and multipolar mitoses. Moderate numbers of phagocytes are evident but there are very few granulocytes.

Spleen: 1800 gm. Architecture obliterated by dense, irregularly arranged collagen. Corpuscles are few in number and markedly shrunken and misshapen, consisting for the most part of a few scattered lymphocytes about the central

arteriole. There is abundant i extracellular hemosiderosis throughout the entire organ. formed, compressed sinusoids p both the sinusoids and fibrosed large numbers of cells similar to t in the liver sinusoids (i.e. both er and myelogenic cells). The mos cells are huge elements with phagocytic cytoplasm. Nuclei mous with prominent nucleoli cells contain 2 to 10, either se fused. Mitotic figures are nun

Bone Marrow: Marrow fat i replaced by hematopoietic cells a There is abundant hemosidero are relatively densely packed a preponderantly of about equal of normoblasts and erythroblas are also large numbers of stem a few granulocytic myelocytes morphonuclears. Many large s with multiple megakaryocyte-li are apparent and are accompanied polar mitoses.

Case 11. C. M. L., 18, female. (

Necropsy: Skin: Marked yello lor with many hemorrhagic areas up to 5 cm.

Serous Coats: Many ecchymos cc. blood-tinged fluid in the cul-de-sac.

Appendiz: Small, 1 cm., he necrotic lesion in middle third of

Lung: Hemorrhagic bronchop with focal necrosis without polyn clear reaction.

Liver: 1400 gm. As in Case 2.

Spleen: 120 gm. Architectu served. Corpuscles normal in nu size but contain numerous stem ticularly aggregated to form a pal collar at the periphery of the nodu soids widened and contain mode bers of phagocytic clasmatoc erythrogenic cells (stem cells, ery and normoblasts).

Lymph Nodes: Enlarged up to mottled reddish gray in appearan licles and germinal centers as i Sinuses are dilated and contain clasmatocytes and scattered l cells. Both of these cells are a

noblasts, erythroblasta and stem
rquently forming. large nodular
Granulopoiesis is scant and there
few true megakaryocytes present.

). P. F. M., 47, male. (FTH #32)
psy: Skin: Pallid; multiple crusted
agic and occasionally purulent
n extremities. Multiple petechial
ages and decubitus ulcers.
: Focal abscess formation with

ardium: 50 cc. of hemorrhagic fluid.
2,000 gm. Kupffer cells very
nt and filled with hemosiderin.
d immature blood cells in the
s.
n: 200 gm. Architecture pre-
corpuscles present but diminished
per. Pulp cords thin and hemor-
Sinusoids filled with moderate
of stem cells, erythroblasts,
cells, normoblasts and clasmato-
There are occasional granulocytes
megakaryocytes.
Marrow: Fat considerably dimin-
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10. F. B., 43, male. (FTH #34)
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ut occasionally granulocytogenic.
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lls, and giant multinucleated cells
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lic cytoplasm. There are many
and multipolar mitoses. Moder-
bers of phagocytes are evident but
e very few granulocytes.
n: 1800 gm. Architecture obliter-
y dense, irregularly arranged
. Corpuscles are few in number
rkedly shrunken and misshapen,
ng for the most part of a few scat-
lymphocytes about the central

arteriole. There is abundant intra- and extracellular hemosiderosis scattered throughout the entire organ. A few deformed, compressed sinusoids persist. In both the sinusoids and fibrosed pulp are large numbers of cells similar to those noted in the liver sinusoids (i.e. both erythrogenic and myelogenic cells). The most striking cells are huge elements with abundant phagocytic cytoplasm. Nuclei are enormous with prominent nucleoli and many cells contain 2 to 10, either separate or fused. Mitotic figures are numerous.

Bone *Marrow:* Marrow fat is entirely replaced by hematopoietic cells and fibrosis. There is abundant hemosiderosis. Cells are relatively densely packed and consist preponderantly of about equal numbera of normoblasts and erythroblasts. There are also large numbers of stem cells and a few granulocytic myelocytes and polymorphonuclears. Many large stem cella with multiple megakaryocyte-like nuclei are apparent and are accompanied by multipolar mitoses.

Case 11. C. M. L., 18, female. (FTH #35)
Necropsy: Skin: Marked yellowish pallor with many hemorrhagic areas measuring up to 5 cm.
Serous Coats: Many ecchymoses and 300 cc. blood-tinged fluid in the peritoneal cul-de-sac.
Appendiz: Small, 1 cm., hemorrhagic, necrotic lesion in middle third of appendix.
Lung: Hemorrhagic bronchopneumonia with focal necrosis without polymorphonuclear reaction.
Liver: 1400 gm. As in Case 2.
Spleen: 120 gm. Architecture preserved. Corpuscles normal in number and, size but contain numerous stem cells, particularly aggregated to form a pale staining collar at the periphery of the nodule. Sinusoids widened and contain moderate numbers of phagocytic clasmatocytes and erythrogenic cells (stem cells, erythroblasts and normoblasts).
Lymph Nodes: Enlarged up to 1 cm. and mottled reddish gray in appearance. Follicles and germinal centers as in Case 4. Sinuses are dilated and contain many free clasmatocytes and scattered large stem cells. Both of these cells are also found in moderate numbers in the edematous lymphoid cords.
Bone Marrow: Both femoral and vertebral marrow fatty and hypoplastic as in Case 1.

Case *12.* A. S., 54, male. (FTH #79)
Necropsy: Skin: Pallid and icteric with many scattered small hemorrhagic areas. Severe gangrenous process in mouth and pharynx.
Heart: Overlying the epicardium is a patchy layer of necrotic fibrin under which is a layer of 1 to 5 large basophilic phagecytic cells, the exact nature of which is indeterminate.
Liver: Swollen Kupffer cella filled with hemosiderin. Moderate central necrosis with some polymorphonuclear reaction.
Spleen: Architecture partially obscured. Corpuscles generally very small, some only recognizable by the presence of the central arteriole, the lymphoid structure having been entirely lost. Such follicles as retain cellularity are now composed only of lymphoblasts, stem cells, and occasionally plasma cells. A few are entirely replaced by fibrous scar. Hemosiderosis ie marked. Billroth's cords are markedly widened by hemorrhagic extravasation, hemosiderin filled phagocytes, or thin strands of fibroblasts. Sinusoids show prominence of littoral cella with focal normoblastic and granulocytic hematopoiesis.
Lymph Nodes: There is increased trabecular fibrosis and vascularization. Sinuses are widely dilated and filled with broad interlacing cords of spindle-shaped epithelioid cells, many of which are phagocytic. Lymph cords are shrunken and in some areas nonexistent. Residual lymphoid tissue is evident as small patches of lymphocytes, among which are phagocytic clasmatocytes and occasional clusters of lymphoblasts and stem cells without any evident germinal center arrangement.
Bone Marrow: Fat cells are markedly diminished in rib and vertebrae and sinusoids are filled with either fibrillar fibroua tissue or large numbers of hemosiderin-packed phagocytes. There are Scattered denselycellular areas of focal hematopoiesis, predominantly erythrogenic, with small nodules of stem cells. Granulocyte forma-

tion is minimal and composed mainly of myelocytes and eosinophiles. Femoral marrow contains more fat and fewer cella than any of the other areas examined.

Case 13. A. V., 51, male. (FTH #80)
Necropsy: Liver: Hemosiderosis of the Kupffer cells and moderate central necrosis.
Spleen: Architecture preserved. Corpuscles normal in number and size but with a collar of immature cells at the periphery. Pulp cords are broad and filled with large amounts of hemosiderin and numbers of phagocytes. The sinusoids are filled with hematopoietic elements which resemble those seen in Case 8, with a predominence of erythrogenic elements, many stem cells and multinucleated cells.
Lymph Nodes: Architecture is preserved and the sinuses are widely dilated. Some contain strands of phagocytic cells attached to and continuous with the lining cells and others contain discrete phagocytes, moderately large numbers of stem cells, and significant numbers of myelocytes. Lymphoid cords are large and edematous. Lymphocytic content is small but there are moderate numbers of stem cells, myelocytes, eosinophiles, apparent lymphoblasts, and active phagocytes without orderly arrangement.
Bone Marrow: Vertebral marrow shows replacement of fat by large dilated interlacing sinusoids. Many of these are filled with erythrocytes, but the majority contain a variety of elements, most of which are stem cells with evidence of differentiation to myelocytes and to a less extent normoblasts. These are frequently arranged in clusters. Hemosiderin, clasmatocytes and normal megakaryocytes are present. There are, however, large numbers of multinucleated giant cells with bizarre mitotic figures similar to those described in Case 10. Femoral marrow is similar qualitatively but is somewhat less cellular and exhibits a background of loose edematous fibrillar tissue.

Case 14. S. M., 62, female. (FTH #81)
Necropsy: Brain: Several subarachnoid hemorrhages over cerebrum and in basal ganglia, the largest measuring 4 x 2.6 cm. involving the thalamus and left lenticular nucleus. Also minute hemorrhages in brain stem.
Skin: Pallid and icteric with numerous small purpuric hemorrhages.
Bladder: Contains large ecchymotic areas.
Pericardium: Contains 150 cc. of bloody fluid.
Liver: Normal size. Histologically negative.
Spleen: Weighs 125 gm. Architecture is preserved but follicles exhibit a variable degree of central degeneration terminating in apparent fibrosis. Surrounding each follicle is a thick collar of lymphoblasts. Hemosiderosis is marked. Sinusoids show prominence of lining cells and occasional small clusters of stem cells.
Lymph Nodes: Lymphocytic content diminished but architecture preserved. There are numerous subsinus aggregations of lymphoblasts. Sinuses are widely dilated and aled with phagocytes.
Bone Marrow: All marrow areas are fatty and show collapsed, empty sinusoids. Each oil immersion field, however, contains one or more sinusoids with compact clusters of 10 to 100 cells which are predominantly normoblasts but are accompanied by moderate numbers of myelocytes, stem cells, and phagocytes with hemosiderin content.

Case 16. W. M., 28, male. (FTH #87)
Necropsy: Skin: Pallid, numerous hemorrhagic areas. Phlegmon of subcutaneous tissues of neck.
Lung: A diffuse hemorrhagic and fibrinous pneumonia with focal necrosis. There are very few granulocytic elements comprising the cellular exudate which consists for the most part of mononuclear phagocytes.
Liver: There is a uniform degree of central lobular necrosis. Sinusoids contain large numbers of myelocytes, eosinophiles, and neutrophilic granulocytes and moderate numbers of primitive stem cells. These are all particularly massed in the center of the lobules, where the sinusoids are widely distended with them. In the extra-endothelial spaces between sinusoids and liver cells there is widespread infiltration by these elementa accompanied by large numbers of phagocytes. The islets

exhibit a slight infiltration with s cells. A 4 cm. soft, yellowish nodule in the gross consists of enormous nu of infiltrating cells distorting and disr the liver parenchyma. These ele are relatively less differentiated thar noted elsewhere in the liver and shov numbers of stem cells and multinuc giant cells with multipolar mitoses to those noted in Case 10.

Spleen: Considerably enlarged, not recorded. Corpuscles are few ir ber and quite small. Pulp architec partially obscured. Recognizable co broadened and filled with erythrocyt hemosiderin. Sinusoids are packec large numbers of myelocytes, stem and multinucleated giant cells. pulp is not evident and there is only phagocytosis.
Bone Marrow: Fat is entirely obli by dense cellularity. Predominan are large myelocytes with intern eosinophilic and neutrophilic pc phonuclears, normoblasts and numbers of stem and giant cells. are numerous mitotic figures and sc throughout are small clusters of cells and erythrocytic precursors.

Case 16. H. L. C., 57, male. #88)
Biopsy: Bone Marrow: Fat con markedly increased and there is degree of fibrosis. Cell content siderably diminished and there ar tered coalescing foci of hemato These consist predominantlyof norm with a few erythroblasts. Megakar are normal and there are diminishe bers of granulocytes with eosinophil tively increased. A striking and feature is the presence of increased r of plasma cells frequently aggregal clusters.

Case 17. L. G., 57, male. (FT
Biopsy: Bone Marrow: The degre lularity is essentially normal. T adequate maturation and the relat portion of white to nucleated red bl is approximately that of normal There are, however, moderately ir numbers of eosinophilic elements a

Also minute hemorrhages in brain

Pallid and icteric with numerous puric hemorrhages.

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Nodes: Lymphocytic content di- but architecture preserved. numerous subsinus aggregations oblasts. Sinuses are widely di- filled with phagocytes.

Karrow: All marrow areas are show collapsed, empty sinusoids. nmersion field, however, contains e sinusoids with compact clusters 0 cells which are predominantly ts but are accompanied by moder- rs of myelocytes, stem cells, and s with hemosiderin content.

W. M., 28, male. (FTH #87)

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here is a uniform degree of ular necrosis. Sinusoids con- numbers of myelocytes, eosin- d neutrophilic granulocytes and lumbers of primitive stem cells. all particularly massed in the he lobules, where the sinusoids distended with them. In the helial spaces between sinusoids lls there is widespread infiltra- ese elementa accompanied by ers of phagocytes. The islets exhibit a alight *infiltration* with similar cells. A 4 cm. soft, yellowish nodule noted in the gross consists of enormous numbera of infiltrating cells distorting and disrupting the liver parenchyma. These elementa are relatively less differentiated than those noted elsewhere in the liver and show large numbers of stem cells and multinucleated giant cells with multipolar mitoses similar to those noted in Case 10.

Spleen: Considerably enlarged, weight not recorded. Corpuscles are few in number and quite small. Pulp architecture is partially obscured. Recognizable cords are broadened and filled with erythrocytes and hemosiderin. Sinusoids are packed with large numbers of myelocytes, stem cells, and multinucleated giant cells. Splenic pulp is not evident and there is only slight phagocytosis.

Bone Marrow: Fat is entirely obliterated by dense cellularity. Predominant cells are large myelocytes with intermingled eosinophilic and neutrophilic polymorphonuclears, normoblasts and large numbers of stem and giant cells. There are numerous mitotic figures and scattered throughout are small clusters of plasma cells and erythrocytic precursors.

Case 16. **H. L. C.,** 57, male. **(FTH #88)**

Biopsy: Bone Marrow: Fat content is markedly increased and there is a slight degree of fibrosis. Cell content is considerably diminished and there are scattered coalescing foci of hematopoiesis. These consist predominantly of normoblasta with a few erythroblasta. Megakaryocytes are normal and there are diminished numbers of granulocytes with eosinophiles relatively increased. A striking and unusual feature is the presence of increased numbers of plasma cells frequently aggregated into clusters.

Case 17. L. *G.,* 57, male. (FTH #10)

Biopsy: Bone Marrow: The degree of cellularity is essentially normal. There is adequate maturation and the relative proportion of white to nucleated red blood cells is approximately that of normal marrow. There are, however, moderately increased numbers of eosinophilic elements and scattered foci in which stem cells or normoblasts are aggregated into small clusters.

Case 18. S. S., 41, male. A 41-year old Russian furniture finisher was admitted complaining of breathlessness.

The patient had been a furniture finisher for 20 years during which time he had frequently been exposed to benzene in paint remover. For about 6 weeks beforeentry there mas fatigability and progressive weakness. Four weeks prior to admission the patient was compelled to give up work but thereafter suffered from dyspnea with the slightest exertion. He developed dizziness, throbbing headaches, nausea and marked palpitation. He had suffered from occasional nosebleed. Examination showed a very marked lemon yellow pallor of the skin. There were small retinal hemorrhages and scars.

Laboratory Findings: The red blood count was 1,380,000, with 50% hemoglobin. The white cells numbered 2,900, with 21% polymorphonuclears, 26% lymphocytes, 1% eosinophiles, 6% monocytes, 36% myelocytes, 2% basophils and 8% unclassified cells. The platelets were reduced. Occasional megaloblasts and normoblasts were seen. Reticulocytes were 2%. The bleeding time was 15 minutes and the clotting time 14minutes. Clot retraction was poor.

On the 14th hospital day a splenectomy was performed. The patient progressed downhill, however, and died on the 46th day in the hospital.

Resection: Spleen: Malpighian corpuscles persist but are markedly compressed and distorted. Pulp and sinusoids are gorged with large clusters of stem cells, erythroblasts and normoblasts. The appearance is similar to that noted in Case 8 but scattered among the erythrogenic foci are moderate numbers of myelocytes and neutrophilic and eosinophilic polymorphonuclears. Mitotic figures, though present, are not overly numerous and there are only small numbers of multinucleated giant cells. Hemosiderin is distributed generally, for the most part within large phagocytic mononuclears.

Necropsy: Bone Yarrow: (Femur) Much of the marrow is fatty but there are large areas with dense cellularity in which prac-

tically no fat is apparent. In the less cellular areas an abundance of fine, eosinophilic fibrillar material is found filling the sinusoids. Elsewhere hematopoietic hyperactivity is apparent with large numbers of mitotic figures, a predominance of young erythrogenic elements, but significant numbers of granulocytic cella as well. Megakaryocytes are unusually scanty and there is only a minimal amount of hemosiderosis.

Case 19. C. deF., 12, male. A 12-year-old schoolboy entered a hospital complaining of weakness of nearly a year's duration.

The patient's father was a painter and the boy spent much time in his father's shop, frequently using a paint remover known to contain benzene. The degree and duration of exposure could not be determined with any accuracy. Severe epistaxis preceded his entry to the first hospital, where examination showed only pallor, a very alight generalized lymph node enlargement, retinal hemorrhages, and a systolic murmur over the heart.

Laboratory Findings: The red cell count was 900,000, with 25% hemoglobin. The white cells varied from 5,000 to 12,000, the blood smear containing only 13 to 16% polymorphonuclears and many lymphoblaete. A sternal puncture was interpreted as confirming the diagnosis of aleucemic leucemia.

Multiple transfusions caused moderate clinical improvement and the patient was discharged. One week after diecharge he entered the Chelsea Memorial Hospital, where physical examination was found to be unchanged. While there his hemoglobin varied between 35 and 75%, rising after transfusions. The red cells ranged from 1,770,000 to 4,140,000 and the white cells from 7,100 to 11,400. The blood smear contained 20 to 47% polymorphonuclears and 51 to 75% lymphocytes. An occasional myelocyte was seen and platelets were decreased. A biopsy from the sternum was performed.

Biopsy: Bone Marrow: There is intense cellularity with only a rare fat vacuole remaining. The cells are almost all lymphoblasts. They are relatively uniform in appearance, measuring 7 to 10 μ in diameter and containing vesicular nuclei within each of which may be found a single nucleolus. The cytoplasm is scanty and homogeneous. Granulocytic elements and nucleated red cells are rare and no megakaryocytes are apparent. Mitotic activity is moderate in degree. There is very slight hemosiderosis.

Summary

Histologic material from 19 patients with a history of chronic *exposure* to benzene (14 autopsies and 5 biopsies) has been described and analyzed. It has been shown that not merely the bone marrow but the entire hematopoietic system characteristically shows changes. The picture in the bone marrow varies from severe hypoplasia to the most extreme hyperplasia and extramedullary hematopoiesis, and in contrast to prevailing opinion, hyperplasia has proved the more common of the two reactions. It has been found only in patients with prolonged exposure, whereas hypoplasia may follow either short or long contact. Sex appears to play an important role—hyperplastic reactions being distinctly more common in the male, hypoplastic ones in the female. In certain of the hyperplastic cases degrees of proliferative activity, of anaplasia and of atypicality of the hematopoietic elements not only in the marrow but in the extramedullary foci have been described which can be distinguished from neoplasia only with difficulty. Finally, 2 cases with typical leucemic pictures, one with frankly neoplastic tumor formation, have been reported and the cumulative evidence linking benzene with the production of leucemia has been discussed.

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