VOLUME XXX • NUMBER 10 • MARCH 1958

UNIVERSITY OF MINNESOTA

Medical Bulletin

OFFICIAL PUBLICATION OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
THE MINNESOTA MEDICAL FOUNDATION
AND THE MINNESOTA MEDICAL ALUMNI
ASSOCIATION

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University of Minnesota Medical Bulletin

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VOLUME XXX March 15, 1959 NUMBER 10

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Published semi-monthly from October 15 to June 15 at Minneapolis, Minnesota

Staff Meeting Report

Hazards of Ionizing Radiation*

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Out of this nettle, danger, we pluck this flower, safety.
SHAKESPEARE, *King Henry IV*, Part One

The scholarly paper of Roentgen announcing the discovery of the x-ray was met by public clamor probably unprecedented in the annals of scientific endeavor. Along with almost frenzied acclaim, bizarre fears and wild claims were expressed and circulated in the world press. A New York City newspaper announced that x-rays were being used at the College of Physicians and Surgeons to reflect anatomical diagrams directly into the brains of medical students, and a New Jersey assemblyman introduced a bill in the state legislature to prohibit the use of x-rays in opera glasses.[1]

The announcement of the atomic attack on Hiroshima with its unloosing of massive new forms of radiant energy brought this problem once again to the attention of a wide public. Great advances in our information concerning ionizing radiations had been made in the interval, and the debate has been tempered by this knowledge. None the less, an element of hysteria has been noticeable in some of the public discussions of this issue. This inquiry will attempt to assess the present status of our knowledge, to learn what implications this knowledge has for the medical profession and particularly for the specialty of radiology, and to indicate some lines of further investigation.

That this review should be a function of the radiologist (as well as of others) seems clear. As has been pointed out by George Tievsky:[2]

> No other scientific discipline has our experience in the use of radiation; no branch of science possesses a comparable experience in dealing with the hazards of radiation; no discipline is so concerned with the interaction of radiation and the whole individual as is ours.

It should be noted here that radiologists have been active for many years in efforts to protect the individual and the population as a

*This report was given at the Staff Meeting of the University of Minnesota Hospitals on February 27, 1959.
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whole against the effects of excessive man-made radiation. Beginning in 1931, when the National Committee on Radiation Protection made its first recommendation of a maximum permissible dose for radiation workers, this problem has been the subject of periodic revision.

In a sense, the current furor over the genetic implications of ionizing radiations is a measure of the progress we have made in conquering the gross hazards of ionizing radiation to the individual organism. Although Roentgen's experiments defined the physical properties of the x-ray in considerable detail, the biological effects of radiation were entirely unknown. A measure of the ignorance of the early radiation workers may be gathered from the remarks of Thomas Edison concerning an attempt of his to utilize the fluorescent effect of x-rays as a means of illumination:[3]

> I started in to make a number of these lamps, but I soon found that the x-ray had effected poisonously my assistant, Mr. Dally, so that his hair came out and his flesh commenced to ulcerate. I then concluded it would not do, and that it would not be a very popular kind of light, so I dropped it.

Most of the early information on the effects of large doses of ionizing radiations was obtained by radiation workers as the result of the inadvertent exposure of their own bodies to the roentgen rays. This is an indication not only of their ignorance but also of their fortitude and perseverance in the face of personal tragedy.

Nowadays, the sort of radiation dosage to which the radiologic pioneers subjected themselves is no longer a problem. Only in rare industrial accidents, in the prosecution of war, and in certain therapeutic situations (where a calculated risk must be weighed against the ravages of cancer) are doses of great magnitude applied acutely to humans. With these situations we are not here concerned. This paper is concerned rather with the possible deleterious effects of low dosages of radiation, applied to individuals over long periods of time or to large populations.

There are two ways in which radiation of this sort has been incriminated. One is somatic damage to the individual. The other is the genetic problem of the weakening of the race by deleterious mutations.

The Somatic Problem

Ionizing radiation in low dosage has been implicated in the production of leukemia, in carcinoma of the thyroid in children receiving radiation therapy to the thymus, in a decrease in fertility, and

TABLE 1
INCIDENCE OF LEUKEMIA AMONG PHYSICIANS, 1929-1948

	Total deaths	Deaths from Leukemia
Nonradiologists	65,922	334
Radiologists	299	14

more generally in a lowering of viability of the organism expressed as a reduction of life span.

Leukemia was reported in radiation workers as early as 1911.[4] In 1924 Carman[5] reported the first death from leukemia in an American radiologist. The subject of leukemia among radiologists has been of intense interest in this country. In 1950 H. C. March[6] compared death rates from leukemia over a 20-year period for radiologists and for other physicians. The data are presented in Table 1. The total number of radiologists for whom leukemia was reported as a cause of deaths is 14. This was reported also as an incidence of 4.7 per cent (compared with 0.5 per cent for all other physicians in the same period) and as an increase of more than nine times. The last has been widely quoted as indicating that the risk of developing leukemia is of the order of nine or ten times greater among radiologists working today, than among nonradiologists. However, as Braestrup[7] has pointed out, March's figures include a large number of the earlier radiologists who, working without protective equipment, almost undoubtedly absorbed doses of radiation in excess of 100r a year. This is 20 times the presently accepted annual maximum permissible dose for radiation workers (Table 2). It may be assumed then that the

TABLE 2
MAXIMUM PERMISSIBLE DOSE RATES FOR RADIATION WORKERS IN ROENTGENS

	Day	Week	13 weeks	Year	Age 20-30
1931	0.2				
1936	0.1				
1949	0.05	0.3			
1956	0.05	0.3	3.0	5.0	50
		In one week			
		0.1			
		Per week/year			

chance of the radiologist developing leukemia as a result of chronic irradiation is considerably less now than indicated by the figures of March.

There is other evidence pointing to x-irradiation as a cause of leukemia. Patients treated for ankylosing spondylitis have an incidence of leukemia between five and nine times as high as the spontaneous incidence of the disease.[8] Children treated for "thymic enlargement" have shown an incidence of leukemia of about 0.5 per cent (eight children out of 1721 traced).[9] Brues[10] has pointed out that these are for relatively large doses of radiation—exceeding 450r in the spondylitis patients and averaging 200r in the thymus patients —given over a relatively short period.

The incidence of leukemia in survivors of Hiroshima has been studied in some detail.[11,12] Among those within 1500 meters of the hypocenter there is a clear-cut increase in the leukemia rate (Table 3).[13] Beyond this range the evidence that there has been any increase in the rate of leukemogenesis is much less convincing. Again, here, it has been calculated that in the area where distinct evidence of an increase in leukemia has been found, a dose in excess of 125 RADs was applied to the individuals involved.[10]

Stewart *et al.*[14] have shown a suggestive increase in the leukemia rate in children whose mothers underwent pelvimetry during gestation. However, other workers have reported findings indicating no evidence for such a relation.[15]

On the basis of evidence of this sort, Lewis[16] has proposed that leukemogenesis is a nonthreshold response to radiation and that radiation-induced leukemia may result from a somatic gene mutation. In

TABLE 3
LEUKEMIA IN RESIDENTS OF HIROSHIMA

Distance from hypocenter (meters)	Number of cases of leukemia With Significant radiation complaints	Without	Incidence 100,000/year
Less than 1000	14	2	175.8
1000 - 1499	15	13	35.2
1500 - 1999	2	4	4.2
2000 - 2499	1	1	1.5
2500 or greater	0	8	2.1
Total	32	28	8.1*

*Leukemia incidence in U. S. A. (White) 6.1/100,000/year

addition, he stated that between 10 and 20 per cent of spontaneous leukemia can be accounted for on the basis of natural background radiation. More recently, Brues[10] has analyzed the data in some detail and concludes that, "Present data on human leukemogenesis by radiation fail to indicate a linear relation between dose and effect. Because data are scanty, such a hypothesis cannot be ruled out statistically, but it is less probable than a nonlinear or threshold relation. . . ."

Radiation has been incrimated in the production of several other tumors. Perhaps the most significant is the association between radiation therapy to the mediastinum or neck in childhood and the development of carcinoma of the thyroid. Clark[17] has reported 15 cases of carcinoma in children receiving irradiation for a variety of reasons, with dosage varying between 200 and 725r. More recently, in a series of 1,502 children treated for thymic enlargement, 10 instances of development of carcinoma of the thyroid were found, whereas in 1,933 siblings no instances of thyroid neoplasm had occurred.[18] In the group in which the neoplasm developed the dose given ranged from 250 to 1400r. It is noteworthy that in all these patients the doses given far exceeded the usual diagnostic range.

There is no evidence that radiation workers currently in the reproductive age range have suffered any loss of fertility. Indeed, a survey on this subject shows a slightly larger number of children in the families of radiologists than in the families of other physicians.[19]

Perhaps the most serious question in regard to somatic damage due to chronic radiation is that of shortening of the life span. Basing his statements on calculations from animal experiments, Hardin Jones has been quoted as stating that one roentgen (of whole body radiation) shortens the life span by 15 days.[20] This appears to be an extreme position. There is no dobut that acute irradiation of animals results in a decrease of longevity.[21] Much of this work, however, has involved large doses of x-radiation and the results do not appear directly applicable to man. On the basis of extensive experiments using both whole and partial body irradiation to mice, Kallman and Kohn[22] point out ". . . how tenuous the quantitative estimates of life shortening in man must be when based on the relatively incomplete data currently available for experimental animals."

In a recent publication, Shields Warren[23] analyzed deaths in groups of radiologists and other physicians over a 25-year period. He found the average age of death of physicians not using radiation in their practices to be 65.7 years, while that of radiologists was 60.5

years. Not only did the radiologists die earlier on the average than non-radiologist physicians but, he stated, "they die younger from practically every cause of death."

These data have been disseminated widely, especially in publications of the National Academy of Sciences.[24,25] But they may be questioned from two points of view: (1) As Braestrup[7] has mentioned, many or most of the deceased radiologists included by Warren had used nonprotective radiation equipment for considerable portions of their careers. It may be calculated that their average lifetime exposure was of the order of 2000r. If reduction in life span is proportionate to dose received, those radiologists now living and receiving radiation within the presently established maximum permissible dose rate of 5r/year (less than 200r in 30 years) should show a decrease of longevity from this cause of about one half of one year (Table 2); (2) In addition, a reworking of Warren's data has shown that the difference in average age of death of the two groups can be accounted for on the basis of differences in the age composition of the two groups (radiologists as a group being younger than physicians as a whole.)[26]

A reworking of Jones' data by Failla indicates that at the level of radiation permitted currently, the theoretical average decrease in longevity for the radiologist should be of the order of two-thirds of a year.[20] This agrees quite well with the extrapolation from Warren's data that can be made using Braestrup's calculations of dose rates. It appears clear that although there may be some shortening of life for radiologists it is very slight at present levels of radiation, and has virtually no significance in patients receiving diagnostic radiation.

The Genetic Problem

In 1927 and 1928 Muller and Stadler independently established that ionizing radiation causes genetic mutations.[27,28] Muller's work was with *Drosophila melanogaster,* and Stadler's with barley. Since that time the bulk of the pertinent work has been performed using the fruit fly, but a sizable number of experiments have been performed utilizing mice and rats.[29]

Although Muller pointed out the possible implications for medical radiology implicit in his initial work, it was not until after the atomic explosions over Hiroshima and Nagasaki that the genetic problems associated with radiation began to be appreciated seriously. The impetus for the renewed discussion of these effects came from the program of atomic and hydrogen bomb explosions being carried out

by several governments, but it soon became evident that at the present time the most significant source of radiation for the human population is from medical uses. This has led to the intense discussions concerning the potential genetic hazards of this radiation that are going on today.

Microscopically visible aberrations in chromosomes from radiation are due to intense radiation and are rarely serious from a genetic point of view since they are associated with temporary sterility or result in lethal mutations and are consequently eliminated.[30] Of greater significance are point mutations which are often nonlethal and are thought by many geneticists to be due to the transfer of energy of one quantum of radiation. This then is felt to be a nonthreshold response, linearly dependent on dose and unrelated to time distribution (Fig. 1). Almost all mutations are deleterious in nature[30] (Table 4). It is important to note that almost all the work done with drosophila and mammals has been with large doses of radiation, much of it in the range above 300r, although linearity has been demonstrated down to 25r in acute experiments.[31,32] More recently, how-

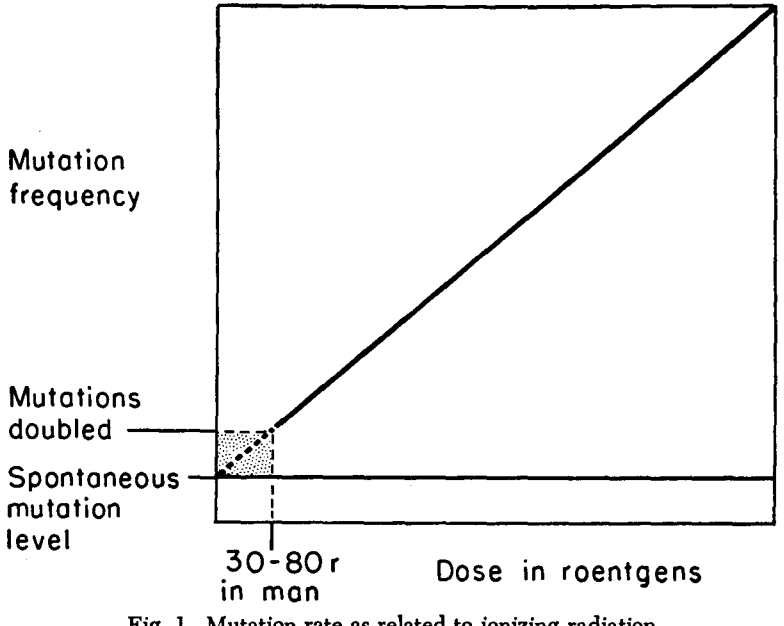

Fig. 1. Mutation rate as related to ionizing radiation

TABLE 4
EFFECTS OF MUTATIONS IN THE DROSOPHILA*

Lethal or sublethal	25%*
Sterility producing	15 - 20%
Subvital	55%
Advantageous	0.1 - 1.0%

*Approximate figures estimated by Glass

ever, experiments on the mouse at low dosage rates have thrown considerable doubt on the theory of linearity between dose and mutation frequency[33] (see p. 299).

The exact fashion in which ionizing radiation effects mutations is unknown. While it has been claimed that the effect is directly on the desoxyribose nucleic acid "coding material" in the chromosomes, radiation has been shown to produce mutations more effectively in an atmosphere of oxygen than in air.[30] This and other similar experiments imply an indirect action of the radiation mediated by one or more chemical steps.

Some, though by no means all, naturally occurring mutations are thought to be due to background radiation. For the fruit fly, radiation has been estimated to account for 0.001 per cent of the natural mutation rate. All people always have been exposed to ionizing radiation, estimated to be of the order of four REM in 30 years[34] (Table 5). This is, of course, an average figure, subject to considerable variation. For example, intensity of cosmic radiation varies strikingly with elevation above sea level, that at Denver being almost twice that at sea-level cities in the same latitude. Individuals living in brick houses receive twice as much radiation from this source as those in houses of wooden construction. Although the radiation from the earth it-

TABLE 5
ESTIMATED VALUES FOR IRRADIATION OF THE GONADS FROM NATURAL SOURCES IN REM/30 YEARS

1. Cosmic Radiation	1.0
2. Earth Radiation (Radium, Uranium, Thorium, Radon and Potassium)	
a. Out of doors - 1/4 of 30 years	0.5
b. Indoors - 3/4 of 30 years	2.0
c. Radon in air	0.2
3. Internal Radiation (K-40 & C-14)	0.5
Total	4.2

self is thought not to differ greatly in different regions,[34] certain areas, such as Travancore in India, show a highly significant increment in radiation from this source.[35] Indeed, Glass[28] has indicated that the 30-year gonadal dose in this region may be as high as 50-150r.

The dose of radiation for the human population at which the rate of mutations would be doubled (the doubling dose) is not known. But, on the basis of calculations involving: (1) the mutation rate in drosophila and mice, (2) the relative size of the gonadal tissue in such animals in relation to the size of gonadal tissue in the human, and (3) the relative life spans of these species, an estimate of the dose as being in the range of 30-80r / 30 years has been made.[25] On this basis a maximum permissible gonadal dose of radiation has been established for the population as a whole: This is 10r in the first 30 years of life in addition to the background radiation.[25] This does not preclude an individual's receiving a larger dosage if necessary for his health, nor on the other hand does it mean that this is a non-mutagenic dose. The UN Scientific Committee on the Effects of Atomic Radiation has indicated that it would be "prudent" to limit the average gonadal dose from medical procedures to the order of magnitude of the background radiation.[36]

It has been estimated by Laughlin and Pullman[37] that the average gonadal dose for diagnostic radiologic procedures for 30 years in this country is 4.1r (Table 6). Estimates for other countries are considerably less; for England and Wales, about one-fifth the American figure. Again, the figures cited are estimates of averages. Many individuals receive amounts much less than this figure while other persons who have been ill have received more.

It is clear from these computations that we are already using all that is "prudent." If the estimates of dosages are correct, and if the theoretical concepts of linearity of dose-mutation frequency and lack

TABLE 6

AVERAGE GONAD DOSE FROM MEDICAL DIAGNOSTIC RADIATION (IN ROENTGENS)/30 YEARS

Radiography	1.8
Fluoroscopy	1.5
Photofluorograms	0.006
Dental X-rays	0.1
Obstetrical X-rays	0.7
Total	4.1

of threshold for radiation-induced mutations are to be accepted, then ways of reducing the dose per examination should be found. The geneticists and other scientists involved in this work are well aware of the vast benefits that the use of ionizing radiations has brought the human race in terms of accurate diagnosis and of treatment. Neither the National Research Council nor the UN Committee has suggested that the medical uses of radiation be abandoned. Indeed, the latter group states that "the medical use of radiation is clearly of the utmost value in the prevention, diagnosis, investigation and treatment of human disease. . . ."[34] As Bentley Glass[30] has pointed out:

> Competent radiologists have assured members of the Genetics Committee that it should be possible to reduce the average exposure of our United States population by at least half without diminishing the needed medical and dental diagnostic information. . . . With prudence and the aid of new developments in radiology which are just around the corner, it may even be possible to reduce diagnostic exposures to one-tenth of the current level, at which point they would become a minor problem.

Recent work has thrown doubt on the linearity of the relationship between radiation at low doses and mutation frequency. Working with mice at a relatively low intensity of radiation (10r per week), Russell, Russell, and Kelly[33] have shown that there is a "much lower mutation rate from chronic gamma than from acute x-irradiation." They conclude that, "From a practical point of view, the results indicate that the genetic hazards, at least under some radiation conditions, may not be as great as those estimated from the mutation rates obtained with acute radiation." In addition, their experiments can be interpreted as throwing some doubt on the belief that the mutagenic response to radiation is a nonthreshold phenomenon. It would seem that any of the following three hypotheses concerning this relationship can be maintained within the area of the doubling rate (Fig. 2): (a) a linear nonthreshold response, (b) a nonlinear response; or (c) a threshold response, below which mutagenic effects will not occur. While keeping in mind the possibility that low doses of radiation may result in significantly fewer mutagenic effects than previously believed, it seems wise for the present to assume the existence of a most serious alternative, namely, the nonthreshold linear relationship.

Discussion

While the exact relation between radiation and its somatic and genetic effects cannot be stated with certainty, it appears clear that

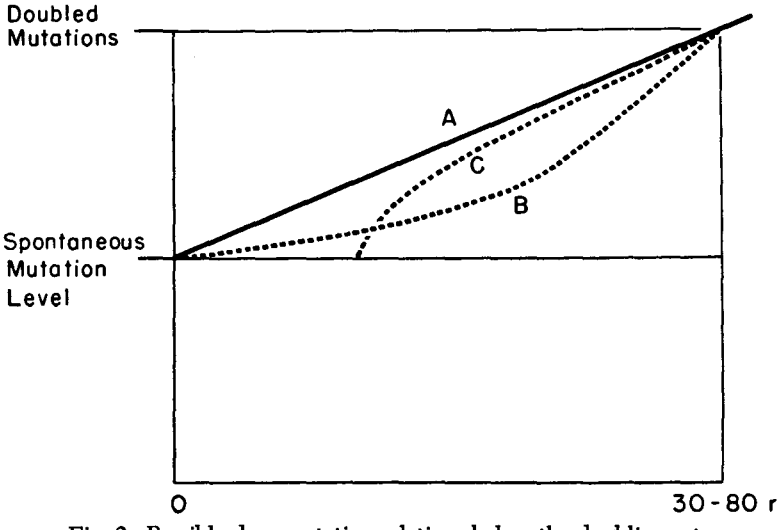

Fig. 2. Possible dose-mutation relations below the doubling rate

dose rates must be kept to the minimum consistent with the effective use of radiation as a diagnostic and therapeutic tool.

The problem of significant somatic injury affects most acutely those working with the medical and industrial uses of ionizing radiation. In an effort to discover the order of magnitude of radiation dosage to some practitioners of radiology at the present time, an analysis of records of several members of the staff of the University of Minnesota Department of Radiology was undertaken (Table 7). Film badges worn for periods of two weeks were reviewed, and in each case dosages were recorded for an entire year. In the case of radiologists number one, two, and three, selection was entirely at random, except that in each there was assurance that the radiologist did in

TABLE 7

DOSAGES IN MILLIROENTGENS RECEIVED BY FOUR STAFF RADIOLOGISTS AT THE UNIVERSITY OF MINNESOTA

Radiologist	1	2	3	4
Total for one year	590	245	295	3915
Average weekly	11.3	4.7	5.7	75.3
Highest dose in two weeks	70	20	80	460

fact wear the badge. Radiologist number four was selected as having consistently the highest dosage rate during the period studied.

A number of problems are involved in the use of film badges for survey work, and the specific readings obtained are probably not of a high order of accuracy. Nevertheless, it is clear that each of the first three radiologists received a dose strikingly lower than the most stringent permissible dose rates. The situation of radiologist number four is a special one: In part, the high readings recorded for him may represent an artefact, as he was in the habit of wearing his badge on his left shoulder, while the others wore theirs on the jacket lapel. In addition, however, this radiologist differed from the others in his fluoroscopic practices. He was in the habit of using large fields and fluoroscoping each patient rather longer than the others. Although his total radiation dose for the year was also within the limits of the maximum permissible dose, it appears clear that a reduction of dose, both to himself and to his patients, could easily be accomplished by changes in technique.

In regard to the genetic hazard, the challenge that has been laid down to the radiologists is to decrease the amount of radiation used for medical diagnostic purposes, first by a factor of two, and eventually by a factor of ten, without reducing the diagnostic efficiency of the method. That this can be done is indicated by a review of the data on the subject.

Improvements in shielding and definition of beam strikingly reduce the gonadal dose. This is important in all examinations but is of the utmost significance in examinations of the abdomen. It has been estimated that 5 per cent of roentgen examinations in the human male—those of the abdomen—contribute 81 per cent of the male gonad dose.[38] It is particularly simple in men to keep the gonads out of the primary beam, or to shield them by the appropriate use of lead. In women, too, in many instances the pelvis can be adequately shielded during abdominal roentgenography without sacrificing significant information.

The striking reduction in dose that can be achieved by proper filtration of the primary beam has been emphasized many times. Figures for fluoroscopy using various amounts of added aluminum filtration (abstracted from Kirsh[39] in Table 8) show a reduction of almost three times as between one-half and three mm. Al. We have demonstrated an even more striking reduction with the use of image intensification (Table 9). A 16-centimeter phantom with a metal object within it was used as a fluoroscopic object for these measurements.

TABLE 8
REDUCTION IN OUTPUT OF FLUOROSCOPE WITH FILTRATION

Added filter	Output
0	12.2 r / Min.
½ mm. Al.	8.8 r / Min.
1 mm. Al.	6.4 r / Min.
2 mm. Al.	4.0 r / Min.
3 mm. Al.	2.8 r / Min.

TABLE 9
COMPARISON OF CONVENTIONAL FLUOROSCOPE AND IMAGE INTENSIFIER

	Conventional Fluoroscope	Image Intensifier
Factors		
KV	85	75
MA	3.5	0.5
Filtration	3 mm. Al.	3 mm. Al.
In Useful Beam		
Table top— with backscatter	3.2 r / min.	0.44 r / min.
Exit through 16 cm. phantom	0.2 r / min.	0.05 r / min.
Outside Useful Beam		
One foot below center	120 mr / hr. (4 x 4 cm. beam) 600 mr / hr. (25 x 25)	24 mr / hr. (5 cm. diameter beam)
Two feet	40 mr / hr. (4 x 4) 215 mr / hr. (25 x 25)	9 mr / hr.
One foot lateral (Fluoroscopist)	200 mr / hr. (4 x 4) 950 mr / hr. (25 x 25)	35 mr / hr.

Factors of milliamperage and kilovoltage were selected at which the object could be clearly identified. For the conventional fluoroscope the usual period of adaptation and complete darkening of the room was used. For the image intensifier the room was partially darkened, but no period of adaptation other than dimming of room lights was practiced. Under these conditions, a reduction in dosage in the beam of almost eight times in favor of the image intensifier was found.* (In addition, it should be pointed out that the brightness of the image was strikingly better with the intensifier than with the conventional fluoroscope.)

As pointed out by Ardran,[40] additional decreases in radiation dose per radiographic examination can be effected by the use of faster

*I am indebted to Mr. George Campbell, Health Physicist, University of Minnesota, for his help in making these measurements.

films and intensifying screens. Use of higher kilovoltage techniques also decreases the amount of radiation needed per examination.

The striking reduction in dosage that practicing radiologists can achieve by variations of technique has been noted in a careful survey of the methods of various radiologists.[41] Clearly, additional large decreases can be effected, particularly by the use of image intensification for fluoroscopic studies, by adequate filtration, and by adequate protection of the gonads in both fluoroscopic and radiographic studies.

Additional studies of actual dosages received as well as data of a basic nature are sorely needed:

- Poppel[42] has advocated the adoption of a national program of monitoring in the form of individual radiation diaries. This proposal has met with numerous objections and has been rejected by the International Commission on Radiological Protection.[43] However, pilot studies of this sort under controlled conditions might provide more accurate information on the amount of radiation to which the population is actually being exposed.
- Additional methods of dose reduction in medical radiology must be sought.
- Demographic studies in situations where an unusual amount of radiation is received by sizable populations (such as in Travancore) could provide direct evidence on the mutagenic response of human subjects.
- Further studies of mutation rates in mammals under conditions of low dosage radiation of the order to which humans are exposed are essential to determine the validity of the nonthreshold linear relation theory for mutations.

Conclusions

1. Evidence indicates that ionizing radiations may cause certain diseases and may also give rise to mutations.

2. Although the exact relation of dose to effect has not been established, it is clear that the hazards increase with dosage.

3. The medical use of radiation is of the utmost value in the diagnosis and treatment of human diseases.

4. Reduction in dosage rates consistent with the effective use of radiation in medicine can be achieved by the proper application of present knowledge. Neither hysteria nor complacency are appropriate reactions to this challenge. The competent radiologist should be known not for the amount of radiation he uses but for the care he

exercises in the diagnosis and treatment of his patients. The challenge can be met.

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Staff Meeting Report

Anemia and Hemochromatosis*

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This report will describe five cases in which an anemia that had not responded to therapy was found to be associated with pigmentary cirrhosis of the liver. We will discuss the associated abnormalities in the blood and bone marrow, which have been clarified by characteristics visible after histochemical demonstration of intracellular nonhemoglobin iron in dry films of blood and bone marrow as well as in sections of bone marrow. The hematologic features seen in these cases will be compared briefly with those seen in megaloblastic anemias, in hemolytic anemias (including thalassemia), and in aleukemic myelosis (atypical myelogenous leukemia, atypical myelosis, myeloid megakaryocytic hepatosplenomegaly). In addition, the abnormalities in the blood and bone marrow in these five cases will be compared with those seen in one nonanemic patient with hemochromatosis described by Howard, Balfour, and Cullen.[1]

The reasons for the difficulties in differential diagnosis will be elucidated. The similarities between the hematologic changes in the anemic patients with hemochromatosis and those in the nonanemic patient will be stressed, in order to show that so-called idiopathic or primary hemochromatosis may first appear to be an anemia of unknown etiology which has become resistant to therapy.

An attempt will be made to show that a combination of hematologic abnormalities is highly suggestive, if not diagnostic, of hemochromatosis.

The types of therapy employed for the anemia associated with hemochromatosis and for hemochromatosis itself will be reviewed.

Literature

Hemochromatosis[2] (hypertrophic pigmentary cirrhosis or bronzed diabetes) is a condition in which a massive increase in storage iron

*This report was given at the Staff Meeting of the University of Minnesota Hospitals on March 6, 1959.

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is accompanied by portal cirrhosis of the liver. Diabetes mellitus and pigmentation of the skin (melanoderma[3] with some excess iron) are expected members of the classic triad of this disease: They may precede or follow evidence of pigmentary cirrhosis, but they are not essential to the diagnosis. Hypogonadism also frequently—but not necessarily—forms a part of the disease pattern.

Sheldon[2] has reported that only 6 of the 92 patients with hemochromatosis for whom adequate data were available had erythrocyte counts below 2,500,000 per cu. mm. and that the average blood counts ("red cells, 4,107,000 per cu. mm.; haemoglobin 80 per cent") were "almost within normal limits." These findings have led to the assumption that anemia is unusual in hemochromatosis. Judging from the paucity of reports of the association of anemia and hemochromatosis, this assumption is probably true, but anemia has not been excluded as a *possible* important feature of hemochromatosis. Stauffer, Butt, and Dockerty[4] stated, for example, that in 25 patients with primary hemochromatosis, 6 had values for hemoglobin of 14 gm. or more per 100 ml. of blood, and 24 had values of more than 11.4 gm. The lower values surely suggest mild anemia.

Recent reviews[5–8] have described cases in which pigmentary cirrhosis, pigmentation of the skin, and some abnormality in glucose tolerance or clinical diabetes mellitus have apparently followed anemias regarded as aplastic, pseudoaplastic, refractory, hyperchromic macrocytic, megaloblastic, hypochromic, and even anemias associated with chronic lymphatic leukemia (one case) and chronic myelogenous leukemia (one case). The terms "secondary,"[4,6] "exogenous"[5,6] and "secondary (exogenous)"[6] have been applied to the hemochromatosis developing secondary to, and possibly indirectly because of, the anemia. The wide use of different anti-anemia therapies, almost always including oral iron, liver, and, in more recent years, vitamin B_{12}, folic acid, and various hematinics (containing vitamin B_{12}, folic acid, intrinsic factor, and iron in one inclusive capsule) has not adequately controlled the anemia; and in many patients, large numbers of transfusions have been given. The iron from the transfused blood has been incriminated as the possible causative agent in most of the cases of associated hemochromatosis. But in some of these cases, it has recently been shown, either no transfusions were given, or the amount of transfused blood was much too small to account for the excess of iron present.[6,9,10] It has therefore been concluded that in some cases, these massive excesses of iron have been absorbed from the gastrointestinal tract. Absorption studies using radioactive iron have indicated that

iron absorption increases in anemia,[11] despite the possible supersaturation of tissue stores. Similar studies have also indicated that iron absorption increases in hemochromatosis.[10]

It is not possible to decide in which of the cases in the literature (45 accepted by Kleckner, Baggenstoss, and Weir[7]) the hemochromatosis is associated with or sesondary to anemia. As Aufderheide, Horns, and Goldish[5] pointed out, most of them are documented only briefly, and the pathologic changes in the liver are difficult to interpret from the descriptions and illustrations. The changes in the blood and bone marrow are equally difficult to evaluate, for these are often only categorized rather than discussed. It seems obvious, however, that most of the anemias are of the pseudoaplastic, refractory type with normoblastic hyperplasia of the marrow.[8] Cooley's anemia (5 cases)[12–14] and hereditary hypochromic anemias (3 cases)[9,15,16] have been reputed to have preceded the development of hemochromatosis. Koszewski[17] described macromegaloblastic erythropoiesis and a macromegalocytic blood picture in eight terminal patients with hemochromatosis. The response of one additional patient to injections of liver[17] suggests megaloblastic anemia, and the changes in the marrow indicate probable hemochromatosis as well. A few of the anemias have been classified as hemolytic.[4,18–21] Descriptions or some comment upon the changes in the marrow have been provided in 42 cases[4–9,17,19–29] of anemia and hemochromatosis. Eleven[4,8,16,21,27–29] of these were not included in the review of Kleckner and associates,[7] most having appeared since publication of that review.

Of particular interest is the fact that Stauffer, Butt, and Dockerty[4] commented upon the marrows of five patients with idiopathic hemochromatosis, mentioning two with excessive amounts of iron in the reticuloendothelial cells and one with increased plasma cells. Koszewski[17] carefully described the marrow of his nine patients with hemochromatosis and macromegaloblastosis, and claimed that the presence of hemosiderin in plasma cells had specific diagnostic importance. Significantly, he found iron in plasma cells in only two of ten patients with "simple hemochromatosis" who were not anemic. The presence of iron in plasma cells in hemochromatosis had been noticed (R.D.S.) prior to Koszewski's report and was mentioned by Jaffé[30] in 1938. Since Koszewski's patients were in terminal condition and had all had histories of alcoholism, his report has not received great notice, but his descriptions of the changes in the marrow are excellent.

The hemosiderosis of the marrow in hemochromatosis has been

illustrated by Rath and Finch;[31] and Finch and Finch[32] stated that erythrocyte production and destruction proceed at near normal rates in hemochromatosis, and that bone marrow morphology is normal except for excessive iron deposits. They added their belief that the presence of siderocytes in the blood (i.e. one to ten per thousand red cells) reflected excessive red cell storage of iron rather than an abnormality in erythropoiesis. Although they recognized the siderocytosis of Cooley's disease, sickle cell anemia, and Hemoglobin C disease, they did not seem to credit these diseases with any similarity to idiopathic hemochromatosis.

The remarkable increase in the amount of particulate iron within cells of the normoblastic series in patients with anemia and hemochromatosis has probably been recognized even if not reported.* But we have found no specific documentation of this feature in hemochromatosis other than descriptions provided by our group.[33,34] Normoblasts containing particulate iron have been called sideroblasts by Kaplan, Zuelzer, and Mouriquand,[35] who showed that they were increased in hemolytic and megaloblastic anemias as well as in thalassemia major and the anemia of lead poisoning. Bilger and Tetzner[36] provided an illustration of a normoblast and a megaloblast with siderophilic granules, but they studied primarily the siderocytosis of hemolytic anemias and of the postsplenectomy state. Gonyea (1945)[34] made a comprehensive comparison of the number of siderotic normoblasts and siderocytes in the marrow as related to the number of siderocytes in the blood of patients with almost all types of anemia. Her data included counts on Howard's[1] nonanemic patient and on three of the patients included in the present study.

Björkman[37] recently described and illustrated sideroblasts from four patients in each of whom a chronic benign anemia was associated with a remarkably sideroblastic marrow. Of multiple aspiration biopsies, all but one were essentially similar in pattern. Björkman's illustrations showing sideroblasts, vacuolization of normoblasts, and abnormal karyorrhexis are comparable to those for the cases of hemochromatosis presented in this report. There was no evidence of hemolysis in his cases. The serum iron was high in three cases, but not in the fourth. In Case 4, myeloblastic leukemia developed terminally. No splenomegaly, hepatomegaly, or signs of hemolysis were observed. The anemias were slightly macrocytic and normochromic (on the basis of the mean corpuscular hemoglobin concentration, and they proved

*Koszewski (ref. 17a) mentioned iron in the erythroblasts of the bone marrow in anemias, but he neglected to emphasize the remarkable sideroblastosis of hemochromatosis.

refractory to therapy. Two of the patients had rheumatoid arthritis; two had auricular fibrillation. Liver biopsies were not obtained. Björkman claimed that practically every normoblast was found to contain free iron; he likened these sideroblasts to the normoblasts seen in autoradiographs subsequent to tagging with Fe^{59} (as described by Lajtha and Suit[38]). He felt, however, that in his cases the sideroblasts were unusual and abnormal, indicating disturbed intracellular iron metabolism and defective hemoglobin synthesis. The changes noted by Björkman are remarkably similar to those found in the anemic hemochromatotic patients to be described in this report.

Recently Granville and Dameshek[28] reported the interesting case of a hemochromatotic patient in whom a folic acid responsive megaloblastic anemia developed. The bone marrow originally had shown pronounced normoblastic hyperplasis and hemosiderosis, and the blood film had demonstrated puntate basophilic stippling of the red cells; during this time the hemoglobin was 11 gm. per 100 ml., the erythrocyte count was 3,600,000 per cu. mm., and the hematocrit level was 32 per cent. A provisional diagnosis of lead poisoning (not substantiated by later studies of lead excretion) was made. Ten months later, the patient exhibited a grayish-brown discoloration of the skin and hepatosplenomegaly. The diagnosis of hemochromatosis was established by liver biopsy. No evidence of increased erythrocyte destruction was obtained. The course of the anemia over a 14-year period was plotted. Megaloblastic anemia developed nine years after the diagnosis of hemochromatosis had been made. The serum B_{12} level was normal, and pyridoxine therapy was not effective.* Folic acid therapy was associated with a rise of hemoglobin from 8 to 11.2 gm. per 100 ml. in four weeks, with some continued megaloblastosis. Three months later, the hemoglobin was 12.4 gm. per 100 ml.; erythroid hyperplasia persisted in the marrow, but it was normoblastic. This case is of extreme interest because it illustrates two things: (1) that the *mild* anemia of hemochromatosis is associated

*Currently interest is sharply focused on substances which may prove effective in treating anemias accompanied by hypochromia and hyperferricemia. Harris, Wittington, Weisman and Horrigan[39] described the first pyridoxine responsive anemia in a human adult. In 1957 these investigators[10] described two cases of anemia which resisted therapy with iron, vitamin B_{12}, folacin, and leucovorin but responded to the oral administration of liquid extract of liver, U.S.P. (Valentine). They felt that the patient with "secondary hemochromatosis" described by Goldish and Aufderheide[9] showed features similar to those of their successfully treated patients.

with normoblastic hyperplasis and hemosiderosis, and (2) that correctable folic acid deficiency anemia can occur in this disease.

Finch and Barnett (1957)[27] reported an extremely interesting case of hemochromatosis in which the diagnosis was established by therapeutic phlebotomy prior to liver biopsy. (Liver biopsy had been considered inadvisable initially because of a marked prolongation of the bleeding and the clotting time.) Their patient, a 47-year-old man, had pigmentation of the skin and hepatosplenomegaly. Findings procluded: a hemoglobin of 12 gm. per 100 ml.; a hematocrit level of 37 per cent; a total white-cell count of 4,950 per cu. mm., with 33 per cent neutrophills, 53 per cent lymphocytes, 10 per cent monocytes, 2 per cent eosinophils, and 2 per cent basophils. The marrow was moderately cellular and showed a decided increase in hemosiderin, and the serum iron was 244 μg. per 100 ml. In the course of almost uninterrupted weekly phlebotomies of 500 ml. for over two years, the patient improved clinically, the liver and spleen regressed in size, the hemoglobin rose to 14 gm. per 100 ml., and the leukocyte count and differential became normal. After two years, the bleeding and clotting studies were also normal, and the clinical diagnosis of hemochromatosis could then be established by biopsy of the liver. This sequence of events indicates that the mild anemia of hemochromatosis is not refractory in the sense that red cells cannot mature or leave the marrow at a normal rate. With removal of blood (iron), regeneration of erythrocytes and hemoglobin occurred with remarkable rapidity in this patient, just as it had in other hemochromatotic patients subjected to phlebotomy.[1,32]

Case Review

The following cases illustrate clearly the difficulties in differential diagnosis of hemochromatosis by demonstrating the range of variation of somewhat similar features and the number of interpretations that could have been made. The morphologic similarities are sufficiently impressive and sufficiently like those of the one patient with idiopathic hemochromatosis to suggest that all the patients have or have had idiopathic hemochromatosis rather than hemochromatosis secondary to anemia. In all these cases transfusions have increased the degree of hemosiderosis but have not caused hemochromatosis, and splenectomy has not seemed to alter the hemoglobin level. Finally, the successful program of therapeutic phlebotomies in progress in one of the anemic patients (M.S.—Case 1) has illustrated that the anemia of hemochromatosis is not refractory, and that blood-letting may be sufficiently beneficial to be justifiable.

TABLE 2
SUMMARY OF CLINICAL DATA ON FIVE PATIENTS

Patients	Case 1 M.S. 49 F-L	Case 2 R.T. 75 M-D	Case 3 C.L. 60 M-D	Case 4 C.P. 79 M-?	Case 5 O.S. 69 M-L
Initial hemoglobin gm./100 ml.	8-13-46 8.3	4-18-49 6.6	4-6-50 9.2	5-1-52 6.7	3-12-58 9.6
Skin pigmentation	+	+	+	+	+
Hepatomegaly	+	slight	slight	slight	—
Liver biopsy	1 month	4 yrs.	19 days	8 days	6 months
Hemochromatosis	+	+	— (P.M. 4 yrs+)	+	+
Splenomegaly	+	Variable	Variable	—	—
Splenectomy	+	—	—	—	+
Glucose tolerance	Diabetic	Abnormal	Abnormal	Abnormal	Abnormal
Chronic fatigue, weakness	+	+	+	+	±
Dyspnea	—	+	+	—	±
Muscle pain	+	+	+	—	—
Joint pain	+	+	+	—	±
Edema	+	+	—	+	+
Ascites	—	+	—	+	—
Abnormal electrocardiogram	+	+	+	+	+
Blood pressure	98/60	110/70	104/60	110/75	100/50

TABLE 3
RESULTS OF LIVER FUNCTION STUDIES

Patients	Case 1 M.S. 49 F-L	Case 2 R.T 75 M-D	Case 3 C.L. 60 M-D	Case 4 C.P. 79 M-?	Case 5 O.S 69 M-L
Bilirubin—mg./100 ml.					
1 min.	0.3	0.1	0.0	0.3	0.1
Total	2.4	0.7	0.2	2.1	1.3
Cephalin cholesterol	3+	3+	0	trace	2+
Bromsulfalein retention—%	6	4	2	14	10
Serum protein— gm./100 ml.					
Total	6.4	7.5	6.5	5.1	5.6
Albumin	2.3	2.7	3.6	2.6	2.7
Globulin	4.1	4.8	2.9	2.5	2.9
Alkaline phosphatase— Units	2.5 B.	5.3 K.A.	2.1 B.	11.0 K.A.	6.6 K.A.
Cholesterol— mg./100 ml.	88.0	83.0	211.0	124.0	—
Thymol turbidity— Units	4.0	8.0	2.0	1.0	3.0
Prothrombin—Seconds Patient/Control	16.3/12.3	14.9/13.3	13/12	14.9/12.7	15.5/15
Fecal urobilinogen— mg./24 hr.	277	307	134	249	551

TABLE 1

SUMMARY OF PREVIOUS DATA ON FIVE PATIENTS PRIOR TO ADMISSION TO U.M.H.

Patients	Case 1 M.S. 49 F-L	Case 2 R.T. 75 M-D	Case 3 C.L. 60 M-D	Case 4 C.P. 79 M-?	Case 5 O.S. 69 M-L
Age onset of anemia	12	61	53	70	45
Degree of anemia Hemoglobin%	Unknown	40	Unknown	40-70	Unknown
Original diagnosis	P.A.	P.A.	Unknown	P.A.	Unknown
Treatment					
Vitamin B_{12}					+
Iron	+	+	+	+	+
Liver	+	+	+	+	+
Folic acid		+			+
Transfusions					+
DATA AT TIME OF ADMISSION					
Dates	8-13-46	4-18-49	4-6-50	5-1-52	3-12-58
Hemoglobin gm./100 ml.	8.3	6.6	9.2	7.8	9.6
Erythrocytes—M./c.mm.	2.85	3.2	2.75	3.4	2.4
Reticulocytes %	4.0	1.4	1.0	0.2	1.5
Hematocrit %	28.0	23.0	31.0	23.0	29.0
M.C.D.—Micra	7.6	9.2	8.8	8.2	8.1
M.C.V.—cu.micra	100.0	81.0	113.0	71.0	119.0
M.C.H.—Micromicrogm.	30.0	20.6	33.0	23.0	39.0
M.C.C.—%	30.0	28.8	29.6	33.0	33.0

From the clinical and laboratory findings in these five patients presented in Tables 1-3 it can be seen that the disease has been a chronic one and that all diagnoses have been confirmed by the presence of hemochromatosis (pigmentary cirrhosis) of the liver on biopsy (4 cases) or at autopsy (1 case).* All the patients have shown pigmentation of the skin. One patient (-Case 1) has diabetes mellitus adequately controlled with insulin; the other four had abnormal glucose tolerance curves. All had abnormal findings in their electrocardiograms. Two patients have died, one patient is unavailable for follow-up, and the other two patients are relatively well. An autopsy performed on one patient (—Case 3) revealed that in addition to pigmentary cirrhosis, there were large amounts of iron in the epithelial cells of the thyroid, the acinar and ductal cells of the pancreas, and the myocardial muscle cells.

*The authors are indebted to Doctors Robert Hebbel and Paul Lober for initial evaluations of the liver in these cases and to Doctor Hebbel for his evaluation of the group of cases in connection with the present study.

The general findings in the bone marrow and blood of each of the patients are shown in Tables 4-7 and are described below:

Case 1. In Case 1, the changes in the blood and bone marrow (1946) were interpreted as those of hemolytic anemia, probably familial in type. The large number of pigment-containing macrophages and the lack of microanisocytosis despite some spheroidocytosis were considered unusual. This patient was found to have hemochromatosis of the liver at the time of splenectomy (1946), and one of us (R.D.S.) again wondered about the importance of the pigment-containing macrophages which had been observed in the marrow. In 1951, at the time of the second bone marrow biopsy, Doctor Rudi Schmid suggested that iron "stains" be tried again.* A method of demonstrating nonhemoglobin iron even in dry film preparations previously stained with Wright's stain was devised;[41] then the bone marrows from 1946 and 1951 were "stained" and the relative amounts of iron in each compared. Storage iron seemed to have increased, although

*Attempts at "staining" for iron in dry film preparations had been unsuccessful in 1947 when interest was focused upon the macrophages in the marrow of the patient reported by Howard, Balfour, and Cullen.[1]

TABLE 4

HEMATOLOGIC DATA CASE 1

Hosp. No. 49 yr. F. Dates, 1946–Present

Dates Occurrence	1946 Splenectomy	1951 Diabetes	1956 Phlebotomies-to-15.7 L. blood	1957
Hemoglobin—gm/100 ml	8.3	11.5	11.5	10.8
M.C.D.—micra	7.6	7.6	7.4	7.6
WBC/cu mm	5,250	13,400	Increased	9,700
Differential %				
Immature N.	0	0	0	0.7 Pl.C.
Neutrophils	52.8	52.0	30.0	58.0
Lymphocytes	40.6	33.5	55.0	31.0
Monocytes	5.0	0	9.5	8.7
Eosinophils	1.0	0	3.5	0.3
Basophils	0.6	1.5	2.0	1.3
Normoblasts	1/300	3/100	Occ.	1/100
Siderocytes	0	+	+	+
Bone marrow				
(Date of specimen)	8-13-46	8-17-51		11-4-57
Fat %	0.0	1.0		0.5
M.E. %	17.0	8.5		14.0
Differential %				
Normoblasts	79.2	57.6		30.8
N. + Precursors	12.0	34.0		48.3
E. + Precursors	2.0	1.4		0.1
B. + Precursors	0.2	0.4		0.1
Lymphoid	6.6	8.0		18.0
Macrophages	Inc.(+Fe)	Inc.(+Fe)		Inc.(+Fe)
Plasma cells	(+Fe)	1.2(+Fe)		1.7(+Fe)
Tissue mast cells	0	0		0
Siderocytes	+	+		+
Sideroblasts	+	+		+
Serum iron— microgm/100 ml	—	228	216-237	133

TABLE 5
HEMATOLOGIC DATA CASE 2
Hosp. No. Yr. M. Dates, 1949-1953 Died

Dates	1949	1950	1952	1953
Transfusions—Liters				
Whole blood	7.5	15.0	17.5	20.5
Packed cells			11.8	19.5
Hemoglobin—gm/100 ml	7.5	7.5	6.6	8.7
M.C.D.—micra	9.2	8.4	—	8.1
WBC/cu mm	4,800	7,800	Normal	1,850
Differential %				
Neutrophils	62.5	52.0	58.5	30.5
Lymphocytes	24.5	32.0	34.0	64.5 (+Fe)
Monocytes	8.0	11.0	3.5	3.0
Eosinophils	0.0	1.0	2.0	1.5
Basophils	3.0(1-lm)	4.0	2.0	0.0
Immature N.	2.0	Occ.	V. Occ.	0.5 Pl.C.
Normoblasts	1/200	Rare	—	1/200
Siderocytes	+	+	+	+
Bone marrow				
(Date of specimen)	11-30-49	10-27-50	7-22-52	3-31-53
Fat %	Trace	Trace	2.0	4.0
M.E. %	11.0	1.5 (iliac)	8.5	8.0
Differential %				
Normoblasts	55.4	23.8	34.8	36.2
Myeloblasts	2.8	—	0.8	0.6
N. + Precursors	26.6	48.8	52.6	22.2
E. + Precursors	2.8	4.2	1.8	1.6
B. + Precursors	1.6	1.8	0.2	0.6
Lymphoid	10.8	19.6	8.6	35.8
Macrophages	Inc.(+Fe)	Inc.(+Fe)	Inc.(+Fe)	Inc.(+Fe)
Plasma cells	Inc.(+Fe)	1.8(+Fe)	1.2(+Fe)	3.0(+Fe)
Tissue mast cells	+	+	+	+
Siderocytes	+	+	+	+
Sideroblasts	+	+	+	+
Serum iron— microgm/100 ml	—	—	—	190
Sections		Granuloma +Fe		

a large amount of iron had also been present in macrophages and cells of the normoblast series in the specimens from 1946. By 1951, diabetes mellitus had developed, and the diagnosis of hemochromatosis was clearly correct.

Case 2. In Case 2 (1949), the peripheral blood showed remarkable macroanisocytosis, occasional atypical platelets and immature neutrophils, very infrequent myeloblasts, and 2 per cent basophils. Some of the basophils contained red granules. The marrow was remarkably hyperplastic and abnormal in appearance. Some of the developing erythrocytes resembled megaloblasts; megakaryocytes were increased and atypical forms were present; and macrophages and tissue mast cells were increased. The findings were regarded as those of chronic myelogenous leukemia, but nevertheless, efforts were made to exclude the possibility of folic acid deficiency. The pattern remained virtually the same in later biopsies, but basophilic stippling

seemed unduly prominent. When the full possibilities of the pattern of hemochromatosis became apparent, we realized (1952) that the changes had probably *not* been those of leukemia but rather that they would all fit with the diagnosis of hemochromatosis. The liver biopsy in 1953 proved positive, clearly establishing this diagnosis.

Case 3. In case 3 (1950), the bone marrow showed a remarkable normoblastosis with a profound left shift in erythropoiesis. The etiology of a granulomatous lesion seen in the sections was sought but not discovered. The patient's son had tuberculous adenitis, but tuberculosis was not clinically considered probable, and autopsy showed no evidence of tuberculosis. In 1952, before the diagnostic possibility of hemochromatosis had been advanced in Cases 2 and 4, slides from this patient (C. L.) which had

TABLE 6

HEMATOLOGIC DATA CASE 3

Hosp. No. 60 Yr. M. Dates, 1950-1954 Died

Dates	1950	1950	1951	1954
Transfusions—Liters				
Whole blood				12.0
Packed cells				1.1
Hemoglobin—gm/100 ml	9.8	9.2	7.5	4.8-8.7
M.C.D.—micra	—	8.8	7.6	7.8
WBC/cu mm	3,500	4,900	8,650	15,750
Differential %				
Neutrophils	25.5	49.0	28.5	80.0
Lymphocytes	50.5	35.5	26.5	9.5
Monocytes	20.5	15.0	42.5	10.5
Eosinophils	2.0	4.5	0.5	0.0
Basophils	0.0	1.0	2.0	0.0
Immature N.	1.5	—	Occ.	—
Normoblasts	Occ.	—	—	3/200
Siderocytes	+	+	+	+
Bone marrow				
(Date of specimen)	4-14-50	4-26-50	6-25-51	10-18-54
Fat %	Trace	1.0 (iliac)	Trace	0.0
M.E. %	27.0	8.5	18.0	8.5
Differential %				
Normoblasts	37.6	53.6	36.0	28.4
Myeloblasts	1.5	—	1.8	3.0
N. + Precursors	45.1	30.0	48.6	40.6
E. + Precursors	1.4	0.6	0.8	0.8
B. + Precursors	0.0	0.2	0.2	0.0
Lymphoid	14.4	13.4	12.0	15-10.2 monocytoid
Macrophages	Inc.(+Fe)	Inc.(+Fe)	(+Fe)	(+Fe)
Plasma cells	Inc.	2.2 (R.E.)	0.6	2.0(+Fe)
Tissue mast cells	+	+	+	+
Siderocytes	+	+	+	+
Sideroblasts	+	+	+	+
Sections	Granulomata + Fe		Lymphocytic aggregates, no granulomata	
Serum iron— microgm/100 ml	—	—	168	143

TABLE 7
HEMATOLOGIC DATA, CASES 4, 5, AND Ur.*

Patients	Case 4. C.P. 75 Yr. M.844287 Dates 1952–1953	Case 5. O.S. 69 Yr. M. 925293 Dates 1958–Present		Case Ur.* 43 Yr. M. 783024
Dates Occurrence	1952	1958	1958 1 month Post Splx.	1947 Phlebotomies 9.43 L.
Hemoglobin—gm/100 ml	6.7	9.6	10.9	15.5
M.C.D.—micra	8.5	8.1	7.8	—
WBC/cu mm	3,100	5,400	Normal	Normal
Differential %				
Neutrophils	62.0	65.0	63.0	33.0
Lymphocytes	21.5	24.0	20.3	60.5
Monocytes	6.5	5.0	7.0	3.5
Eosinophils	6.0	3.0	6.7	1.5
Basophils	4.0	3.0	3.0	1.5
Immature N.	0.0	0.0	0.0	0.0
Normoblasts	1/200	1/200	2/300	0.0
Siderocytes	—	+	+	+
Bone marrow (Date of specimen)	5-5-52	3-19-58	10-8-58	12-9-47
Fat %	1.5	15.0	10.0	3.8
M.E. %	36.0	34.0	13.0	10.0
Differential %				
Normoblasts	53.4	59.0	39.0	41.5
N. + Precursors	33.4	31.6	39.8	28.4
E. + Precursors	2.2	1.6	4.2	3.9
B. + Precursors	0.0	1.0	0.3	0.0
Lymphoid	10.8	6.8	16.7	26.2
Macrophages	Inc.(+Fe)	Inc.(+Fe)	Inc.(+Fe)	Inc.(+Fe)
Plasma cells	0.2(+Fe)	(+Fe)	(+Fe)	(+Fe)
Tissue mast cells	+	+	+	+
Siderocytes	+	+	+	+
Sideroblasts	+	+	+	+
Sections	Granuloma within lympho-cytic aggregate			
Serum iron— microgm/100 ml		205-30	194	362

*Case Ur. reported by Howard, Balfour, and Cullen[1]

shown prominent coarse basophilic stippling were subjected to the prussian reaction; it was thus established that particulate iron was remarkably increased in the normoblasts and erythrocytes as well as in the macrophages of this patient. The diagnosis of hemochromatosis was suggested. The granuloma was "restained" and found to contain iron. The patient continued to present clinical problems due to his profound anemia and great susceptibility to infection. There is no record of his having received folic acid in the course of his disease. The final specimen of marrow showed more iron and more abnormalities than had the preceding three specimens, with a prominent shift to the left in erythropoiesis and an increase in basophilic normoblasts whose nuclear patterns suggested reticular origin. These changes might have been brought about by a deficiency of folic acid or some other essential anti-anemic factor, but since the patient was moribund at the time

of biopsy, this possibility could not be explored. The diagnosis of hemochromatosis was made from autopsy material by Doctor Robert Hebbel.

Case 4. In Case 4 (1952), the changes in marrow and blood were interpreted as suggestive of hemochromatosis. Sections of the marrow showed a granulomatous lesion. The fact that both this granuloma and that from the marrow of the previous patient contained iron, prompted an exhaustive search for granulomata in the first two cases. As a result, one tiny granuloma which also contained iron was found in the marrow from R.T.—Case 2. The finding that these granulomata contained iron, whereas those of tuberculosis, brucellosis, and sarcoidosis did not, was reported in 1954.[42] Biopsy of the liver was performed, and the diagnosis of hemochromatosis of the liver was made.

Case 5. In Case 5 (1958), the changes in marrow and blood were highly suggestive of hemochromatosis, a diagnosis that was established by liver biopsy six months later. Because life-span studies of the erythrocytes and values for fecal urobilinogen suggested hemolysis, a splenectomy was performed. Neither this procedure nor a recent therapeutic trial of pyridoxine (100 mg. intramuscularly daily for two weeks) has altered the hemoglobin level.

The marrow specimen (1947) from the nonanemic patient with known hemochromatosis described by Howard *et al.*[1] showed normoblastic hyperplasia, slight megakaryocytosis, and a relative and absolute increase in "lymphoid cells." The normoblastosis was not regarded as unusual in a patient with known liver disease. Attention was centered upon the increase in pigment-containing macrophages, the increase in plasma cells, and the presence of pigment in plasma cells. The erythrocytes in the blood showed slight macroanisocytosis, and basophilic stippling was described. In the peripheral blood smear there was a relative (60.5 per cent) and absolute lymphocytosis in addition to the lymphocytosis of the marrow, but the general blood picture did not suggest a diagnosis of leukemia, and sections showed no specific lesion other than the increase in pigment. In the current review of the marrow from this patient, the obvious abnormalities in erythropoiesis which are present have now attained diagnostic significance in comparison with all the other marrow specimens.

Hematologic Changes—Morphology

Bone Marrow

The changes in the bone marrows of all of these patients and in the marrow of the nonanemic hemochromatotic patient are remarkably similar. The marrow is generally hyperplastic, but fat and the fundamental architecture remain. Occasional hypoplastic areas are seen in some of the sections.

Normoblasts and Storage Iron

Normoblasts are remarkably increased in most cases, numbering

from 24 to 80 per cent of the total nucleated marrow cells. A true differential of the percentages of the various developmental stages of cells of the normoblast series is difficult to obtain because there is a remarkable tendency for grouping of normoblasts. Twin and quandruplet normoblasts in identical phases of development are numerous, and nests of normoblasts are common. Attempts at counting mitoses were made, but in these bone marrows, numerous late telophases often cannot be distinguished from twin normoblasts with no visible space between their cytoplasmic boundaries. This feature makes the estimation of the number of mitoses far from accurate.

Some of the marrows show a remarkable increase in pronormoblast, but in most, the shift toward the more mature forms is as prominent as or more prominent than the shift to the left. The most profound shift to the right (great increase in orthochromatic normoblasts) was found in the marrow from the nonanemic patient.[1] Binucleate and multinucleate normoblasts are present. Occasional giant erythroblasts—some of them multinucleate with nuclear patterns comparable to those of megaloblasts—can be found in most of the specimens of marrow. Erythropoiesis seems disorganized: There is sufficient variation in cell size and in nuclear pattern to suggest that one might name these developing erythrocytes normoblasts, macronormoblasts, intermediate cells, and even, occasionally, megaloblasts. The overall abnormalities in the developing erythrocytes, however, seem different from those of most megaloblastic anemias (even in partial relapse or remission). Although an occasional giant metamyelocyte somewhat similar to those of megaloblastic anemia may be found, mature neutrophils often show some lack of granulation rather than the characteristic granulation of the pernicious anemia neutrophil.

In rare instances the normoblasts show perinuclear lakes of hemoglobin comparable to those seen in erythropoietic porphyria.[43] More often, relatively large normoblasts (in the polychromatic stage) with somewhat pyknotic nuclei show fairly abundant filmy cytoplasm which is pale blue rather than polychromatic or orthochromatic. This cytoplasm appears delicate and thin; its pale but darker portions radiate out from the nucleus in a fashion which makes the normoblast resemble a Downey Type II lymphocyte.[44*] The cytoplasm may contain fine basophilic stippling comparable to that illustrated by Kato and Downey,[45] or coarse stippling which proves to be iron,[41]

*For descriptive purposes, these cells are often called Type II normoblasts.

and there may be large spaces or vacuoles comparable to those illustrated by Björkman.[37] Some of these normoblasts probably degenerate; others are probably the immediate precursors of the almost anochromatic leptocytes. The latter cells may contain both precipitated ribonucleic acid and particulate iron. Other abnormalities are also found. There is a type of karyorrhexis in which the karyorrhectic buds are spatulate in appearance, and the karyorrhectic figure may resemble a daisy or, better, the blades of an electric fan. Some of these abnormalities have been described in cases of severe lead poisoning.[46]

Even before the marrow specimens are subjected to the prussian blue reaction, coarse basophilic stippling may be found in normoblasts and in red cells. Subsequent to the prussian blue reaction, however, a surprising number of normoblasts in all stages of development will contain granules of iron which vary from dots of blue green material to huge chunks which are also blue green but have a metallic appearance. The largest particles are found in the more mature cells (polychromatic and orthochromatic normoblasts) and in the siderocytes. The number of normoblasts containing particulate iron (50.0–99.4 per cent)[36] is extremely high in hemochromatosis, but it may be equally high in occasional cases of megaloblastic, hemolytic, or refractory anemia. In general, the size of the particles of iron in normoblasts is greater in hemochromatosis than in other conditions, but even this feature cannot be considered specifically diagnostic.

Granulocytes

None of the features of the granulocytes appears sufficiently abnormal or consistent to have diagnostic value. Neutrophils and their precursors are relatively decreased in number, while myeloblasts and basophils may show a minimal increase.

"Lymphoid Cells" and Storage Iron

"Lymphoid cells" including lymphocytes, monocytes, reticuloendothelial cells, macrophages, and plasma cells are variable in number. Reticuloendothelial cells and macrophages are increased, and phagocytosis of erythrocytes, normoblasts, and pigment is greater than usual. Plasma cells are often increased, sometimes remarkably so. No plasma cell containing a phagocytosed erythrocyte has been found, but plasma cells containing olive- to blue-green pigment have been noted in each of the present five cases and in one of the cases reported by Howard, Balfour, and Cullen.[1]

Islands of normoblasts surrounding reticular cells are prominent.

The intimate union of the cytoplasm of the reticular cells and of the normoblasts is often not destroyed in the process of making the marrow film. Subsequent to prussian "staining," homogeneous blue-green material (ferritin[41]) and blue-green granules, flocculent masses, and crystals of nonhemoglobin iron can be seen in the cytoplasm of the reticular cells. In the cytoplasm of the normoblasts surrounding the reticular cells, tiny granules of particulate iron are also seen. In these preparations it appears as though the granules of iron could pass from one cell to another without difficulty. This semblance of the possible transfer of particulate iron from the reticular cell to normoblasts in any stage of development has been of great interest. The fact that reticular cells do act as "mother" cells in a very real sense by providing iron to the "nursing" normoblasts has been beautifully demonstrated by Bessis,[47] using electron microscopy. (Bessis summarized much of his work in 1958,[47] and presented these and additional findings at the University of Minnesota on January 9, 1959.)

Often the particulate iron in reticular cells and macrophages occurs in large crystals (hemosiderin[48]). Some of these crystals are large enough, and the cells containing them look sufficiently degenerate, for this iron to qualify as a type of nonutilizable iron (goethite, limonite) described by Schwietzer.[49]

Although macrophages containing excessive quantities of stainable iron are present, these cells are often not as numerous in dry films or sections of the marrow in hemochromatosis as they may be in anemias associated with increased storage iron (hemolytic anemias, megaloblastic anemias, anemies of chronic disease such as multiple myeloma, carcinomatosis, etc.). In sections of the marrow, storage iron (in macrophages) is relatively patchy in distribution, a peculiarity that may be reflected in the films of marrow where one specimen shows many more macrophages than does another specimen taken from the same sample of marrow.

The presence of stainable iron in plasma cells was emphasized by Koszewski[17] and mentioned by Jaffé.[30] The masses of iron are reasonably spherical or oval rather than crystalline. They vary in size from small granules to masses about four or five micra in diameter. Since a few of the abnormal normoblasts show a profound resemblance to plasma cells, the presence of "stainable" iron in both cell types is a startling morphologic finding. One would hope that this might prove to be a specific feature in the marrow in hemochromatosis, as Koszewski's comparisons suggest.[17] We have made determinations

for storage iron in special cases since 1951 and routinely since 1955. We now believe that stainable iron in plasma cells has only been found in patients with enemias which could ultimately prove to be associated with hemochromatosis, but some cases of this type in our files await confirmation.

In some of the patients described in this report, monocytes have been increased. Although this causes a problem in differential diagnosis, it appears a fairly frequent finding in hemochromatosis.

In many of the cases, phagocytosed iron has been found in monocytes and neutrophils in the concentrated specimens of marrow. This phagocytosis may have occurred during the time necessary for preparation of these centrifuged specimens. None of the neutrophils show the diffuse prussian positivity of ferritin in its own cytoplasm; the mass of iron appears to have been engulfed, not incorporated within the cytoplasm, as it seems to be in the reticular cells.

Tissue mast cells have been found in the marrow in four of the five patients. In three, they were easily seen; in one, they had to be sought. In the marrow from the nonanemic hemochromatotic patient,[1] an occasional tissue mast cell was found after a determined search.

Megakaryocytes

The number of megakaryocytes has appeared slightly increased in all the cases. Small uninucleate forms apparently derived directly from reticuloendothelial cells, and large multinucleate forms have been seen. Occasional bizarre and atypical platelets have been found in both the bone marrow and the blood.

Blood

The general morphologic changes in the blood have been confusing. As indicated previously,[33] the changes vary from patient to patient, but the blood picture in general shows features which bring to mind the possible diagnoses of: thalassemia minor (basophilic stippling and target cells with variable hypochromasia); megaloblastic anemia (oval macrocytes well filled with hemoglobin, poikilocytosis, and leukopenia with relative lymphocytosis); and aleukemic myelosis[50,51] (poikilocytosis, anisochromia, spheroidocytes, occasional atypical platelets, leuko-erythroblastotic reaction, and increased basophils). The nonanemic patient with hemochromatosis exhibited a relatively simple macrocytosis with occasional hypochromic cells and occasional siderocytes.

Discussion

After carefully reevaluating the general patterns in the bone marrow and blood of these anemic patients with hemochromatosis, and after comparing the general pattern with that of the patient who had hemochromatosis but no anemia, we feel that the abnormality may very well be one of degree. Erythropoiesis is not nearly as disorganized in the bone marrow of the nonanemic patient as in those with anemia. His marrow, however, contains abnormally developing erythrocytes, and many of the abnormalities (including the large amount of iron in plasma cells) seen in the marrows of the anemic patients are present. These features suggest that the anemic patients described here have idiopathic hemochromatosis. Hemosiderosis has probably been enhanced by the administration of oral iron over long periods in all of the cases. The two patients who have died received added iron from multiple transfusions.

The features described here also suggest that the diagnosis of hemochromatosis, with or without anemia, may be strongly suspected on the basis of morphologic findings in the bone marrow and blood. These changes should be associated with an elevation in the level of serum iron. If the serum iron study should prove normal or low, the test should be repeated, for the serum iron may be low in the presence of some infection or for unknown nontechnical reasons. If the hematologic changes and the level of serum iron suggest hemochromatosis, a liver biopsy is, of course, the most acceptable way to establish the diagnosis. But if there is any tendency to bleeding, caution should be exercised as described by Finch and Barnett,[27] who established their diagnosis clinically by therapeutic phlebotomy prior to biopsy of the liver.

Many of the hematologic features seen in the anemia associated with hemochromatosis are comparable to those of megaloblastic anemia. In the latter, however, megaloblastosis is more uniform, and giant precursors of pernicious anemia neutrophils are generally very helpful in diagnosis. Iron has not been found in plasma cells in megaloblastic anemias. The size of the iron particles in the megaloblasts and the megalocytic siderocytes is usually smaller, and target cells are not common in megaloblastic anemia. Occasional megaloblast-like cells or megaloblasts are seen in hemochromatosis. In the marrows of the patients included in this report, the megaloblasts (?) and abnormal erythroblasts have not disappeared with liver, vitamin B_{12}, or folic acid therapy despite the fact that the anemias were re-

puted to have responded to therapy earlier. The defect in erythropoiesis is probably an inherent feature, which is not understood at present. The fact that a frankly megaloblastic component of the anemia may develop, however, seems certain,[17,28] and one of the patients described in the literature responded to liver,[17] and another,[28] to folic acid. In view of the experience of Harris and associates[39] and Horrigan and associates,[40] therapeutic trials of pyridoxine and crude liver extracts may also be indicated.

The anemia associated with hemochromatosis may at least seem to be hemolytic in some cases. The impressive normoblastic hyperplasia surely suggests hemolysis, and in one of our patients (O.S.—Case 5), a decreased life span and an increased amount of fecal urobilinogen also suggested hemolysis. In neither of the patients subjected to splenectomy (M.S.—Case 1, and O.S.—Case 5) does the anemia seem to have been altered by this procedure. In most clear-cut hemolytic anemias, erythropoiesis is less disorganized, reticulocytosis is greater, tissue mast cells are not prominent in the marrow, and plasma cells containing iron are not found. However, the relationship of hemolytic anemia to hemochromatosis requires clarification from disciplines other than pure morphology.

The abnormalities in erythropoiesis are sufficiently comparable to those in erythropoietic porphyria, severe lead poisoning, and thalassemia to suggest that porphyrin metabolism as well as iron metabolism is abnormal.

The relationship between hemochromatosis and thalassemia is too obscure to be clarified briefly, but since patients with Cooley's anemia are reputed to develop hemochromatosis, the subject cannot be ignored. In both conditions, there is defective erythropoiesis, excessive storage iron, and hypochromia of erythrocytes. Further investigations in this area are projected, including studies using starch block electrophoresis[52] on two of the patients with anemia and hemochromatosis.

The relationship between hemochromatosis and aleukemic myelosis or even so-called erythroleukemia is also challenging. For the dysplastic erythropoiesis of hemochromatosis, the occasional abnormal megakaryocytes, and atypical platelets, and the slight increase in basophils seen in hemochromatosis prompted an initial diagnosis of chronic myelogenous leukemia in one of these cases. In aleukemic myelosis and erythroleukemia the normoblasts often appear to contain as much particulate iron as they do in hemochromatosis. The difficulties in differentiating among this group of diseases—from the

standpoint of initial clinical findings, morphologic findings, and often also the elevation of the level of serum iron—are sufficient to suggest the possibility that hemochromatosis itself might be included as one of the myeloproliferative syndromes. This is only proposed as one not *too* impossible idea, emphasizing primarily the extreme difficulty of diagnosis.

Therapy of Hemochromatosis

No effort has been made to review the literature regarding the therapy of hemochromatosis by blood-letting. In the nonanemic patients, removal of iron through phlebotomies has been associated with clinical improvement.[1,32] Finch and Finch[32] claimed that iron deposits in the liver have been removed, and normal levels for plasma iron have been attained; insulin requirements have been reduced, pigmentation decreased, and liver function improved; and cardiac dysfunction in particular *may* be helped.[32] The one patient studied by Howard *et al.*[1] whose hematologic findings are included in this report had improvement of general status, decrease of pigmentation, and decrease in the size of the liver subsequent to the removal of more than 45 gm. of iron during the first four years of treatment. Recently Finch and Barnett[27] have reported a good therapeutic response to venesections in one hemochromatotic patient who was mildly anemic. Prior to the publication of that report, the therapeutic phlebotomies had been carried out as the only hopeful approach in one patient (M.S.—Case 1). The program has been carried out slowly, 500 ml. of blood being removed at two- or three-week intervals with frequent interruptions. To date 21.25 liters of blood have been removed. The patient has had many fewer muscle pains; pigmentation has diminished; her liver, which was massive, has decreased in size remarkably; the patient's insulin requirement has dropped from 70 to 50 units; her hemoglobin ranges around 11 to 12 gm. per 100 ml., rather than 9 to 11; and her total leukocyte count is normal with an almost normal differential. The number of siderocytes in her blood has decreased strikingly.

It is apparent from the response obtained to phlebotomies in this patient and in the patient described by Finch and Barnett[27] that the anemia of hemochromatosis is by no means a refractory anemia in which red cell regeneration and release are impossible. Hemoglobin levels fluctuate even without phlebotomy, but occasionally the hemoglobin has regained its prephlebotomy level in one week, sometimes in two or three.

Summary and Conclusions

Five cases in which anemia unresponsive to hematinics has been associated with hemochromatosis have been discussed briefly.

The literature concerning anemia and hemochromatosis has been reviewed. This review and the recognition of similar abnormalities in the blood and bone marrow of one nonanemic patient as well as five anemic patients with hemochromatosis have led us to believe that hemochromatosis is probably a disease which affects the hematopoietic system in a characteristic manner. When this effect is more severe, it results in an anemia which may be the limiting feature in the disease. In most of the reported cases of idiopathic hemochromatosis, the bone marrow has not been scrutinized carefully, and thus a pattern which seems useful in diagnosis has largely been overlooked.

The anemia that seems to precede the development of hemochromatosis is believed to be an unusual manifestation of idiopathic hemochromatosis, rather than the mechanism which provokes increased absorption of iron and the ultimate development of pigmentary cirrhosis and bronzed diabetes. Although the concept of secondary or exogenous hemochromatosis can probably be rejected, loading of the body with iron may nevertheless have deleterious effects.

The problems in differential diagnosis have been discussed, and the association of one well validated instance of folic acid responsive anemia with hemochromatosis[28] has been emphasized.

Since the possibility of hemochromatosis has been suggested on the basis of morphologic abnormalities in the bone marrow and blood prior to the demonstration of pigmentary cirrhosis in four of the five cases presented here, it is hoped that with further experience, diagnosis may be made before the occurrence of changes which are only partially reversible. The seemingly beneficial effects of therapeutic phlebotomies in one anemic patient with hemochromatosis have been summarized.

Acknowledgments: The authors wish to thank the following people: Dr. C. J. Watson of the Department of Medicine for permission to use the clinical data in the cases reported here: Dr. Robert B. Howard for permission to use, for invaluable comparaitve studies, samples of the bone marrow and blood from one of the patients he has reported; members of the Department of Special Hematology, including Mrs. Harriette Broman Snoga, Miss Lorraine M. Gonyea, Miss Kathryn A. Grave and Miss Ella Spanjers for their interest and assistance; Mrs. Elaine McMasters for help in providing tissue specimens used in this study; Dr. John Penner for his assistance in making important studies on the last patient (O.S.—Case 5) described in this report; Mr. Gordon Herbst for his invaluable help in organizing the format of the tables.

The studies presented here illustrate the type of information that can be derived from correlation of the demonstrations of iron in cells and in plasma. The authors wish to emphasize that the pioneer work on plasma iron in the University Hospital was done by

Dr. Robert B. Howard. Later Dr. Roy G. Holly made important contributions in this field. Currently the plasma iron determinations are a routine service of the chemistry laboratory. The authors wish to thank Miss Esther Freier for her enthusiastic interest and cooperation in making these determinations possible.

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Medical School Activities

DR. HENRY E. MICHELSON, Professor Emeritus, Division of Dermatology, was recently elected to honorary membership in the New York Dermatologic Society. This Society is the oldest of its type in the world and will soon celebrate its ninetieth anniversary.

On March 21, DR. HERBERT M. BOSCH, University of Minnesota Professor of Environmental Sanitation in the School of Public Health, received the University of Missouri's honor award for distinguished service in engineering at Engineering Day activities in Columbia, Missouri. The Missouri award was given "in honor of his continued participation in public health activities, as a member of state, national and international organizations dedicated to the protection and improvement of the health and comfort of the peoples of the world."

DR. LEONARD M. SCHUMANN, Professor of Epidemiology, School of Public Health, has been appointed to the National Cancer Control Committee of the National Cancer Institute, U. S. Public Health Service, for the period of March 1, 1959 to December 31, 1962. Dr. Schumann, as consultant to the National Cancer Institute, also attended a meeting of the representatives of the National Cooperative Leukemia Study Group on February 4, 1959, in Pittsburgh, Pennsylvania.

Coming Events

April 16–18 . . . . . Continuation Course in Allergy for General Physicians and Specialists

April 30 . . . . . HISTORY OF MEDICINE SEMINAR: Dr. L. R. C. Agnew, Chairman, Department of the History of Medicine, University of Kansas Medical Center, Kansas City 12, Kansas

May 11–15 . . . . . Continuation Course in Introduction to Electrocardiography for General Physicians

May 18–22 . . . . . Continuation Course in Proctology for General Physicians

May 27–29 . . . . . Continuation Course in Otolaryngology for Specialists

June 15–17 . . . . . Continuation Course in Gynecology for General Physicians

WEEKLY CONFERENCES OF GENERAL INTEREST

Physicians Welcome

Monday,	9:00 to 10:50 A.M.	OBSTETRICS AND GYNECOLOGY Old Nursery, Station 57 University Hospitals
	12:30 to 1:30 P.M.	PHYSIOLOGY- PHYSIOLOGICAL CHEMISTRY 214 Millard Hall
	4:00 to 6:00 P.M.	ANESTHESIOLOGY Classroom 100 Mayo Memorial
Tuesday,	12:30 to 1:20 P.M.	PATHOLOGY 104 Jackson Hall
Thursday,	11:30 A.M. to 12:30 P.M.	TUMOR Todd Amphitheater University Hospitals
Friday,	7:45 to 9:00 A.M.	PEDIATRICS McQuarrie Pediatric Library, 1450 Mayo Memorial
	8:00 to 10:00 A.M.	NEUROLOGY Station 50, University Hospitals
	9:00 to 10:00 A.M.	MEDICINE Todd Amphitheater University Hospitals
	1:30 to 2.30 P.M.	DERMATOLOGY Eustis Amphitheater University Hospitals
Saturday,	7:45 to 9:00 A.M.	ORTHOPEDICS Powell Hall Amphitheater
	9:15 to 11:30 A.M.	SURGERY Todd Amphitheater University Hospitals

For detailed information concerning all conferences, seminars, and ward rounds at University Hospitals, Ancker Hospital, Minneapolis General Hospitals, and the Minneapolis Veterans Administration Hospital, write to the Editor of the BULLETIN, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minnesota.