15th May, 1953.

This is to certify that the thesis "Radioiron Absorption Studies in Idiopathic Haemochromatosis, Malnutritional Cytosiderosis, and Transfusional Haemosiderosis" presented in partial fulfilment for the degree of Doctor of Medicine at the University of the Witwatersrand, is my own work and has not been presented at any other University.

T. H. BOTHWELL

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RADIOIRON ABSORPTION STUDIES IN IDIOPATHIC HAEMOCHROMATOSIS, MALNUTRITIONAL CYTOSIDEROSIS, AND TRANSFUSIONAL HAEMOSIDEROSIS

by T. H. BOTHWELL, M.B. Ch.B. (Rand)
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A Thesis presented in partial fulfilment of the requirements for the degree of Doctor of Medicine at the University of the Witwatersrand.

MAY, 1953.

TO MY MOTHER.

ACKNOWLEDGEMENTS

At the outset I wish to acknowledge with gratitude the generous support which this work has received from the Council for Scientific and Industrial Research and to recall the happy association with those members who collaborated with me at various stages of this investigation. First and foremost was Miss T. Alper but subsequent invaluable assistance has also been given by Dr. H. van Waalwyk van Doorn-Wittkampf, Miss M.L. du Prees and Mr. D.V. Savage.

In addition, I am grateful to Drs. A.L. Agranat, I.J. Grek, S. Grieve, E. Meltzer, E.M. Popper, M.M. Suzman and V.H. Wilson for access to cases under their care. It is also a pleasure to thank the Pathology Department, University of Witwatersrand and especially Dr. C. Chatgidakis for access to and help with the pathological material. My thanks are also due to Dr. B.C. Ellis who not only performed blood volume and serum iron estimations but also took a keen and critical interest in the work at all stages. To Dr. H.B. Stein and Dr. B. van Lingen, my gratitude for their stimulating and helpful comments and to the librarians, Miss A.C.Dick, Miss M. Lucas, Miss Y. Kemp and Miss D. Thomson my thanks

/for ...

for their unfailing friendliness and help. A special word of thanks is due to my sister, Miss M.F. Bothwell, for help in the preparation of the graphs and to Mrs. B.C. Ellis for her selfless typing.

This study was initially stimulated by the work of Professors J. and T. Gillman and by their kindly interest and help at all times. Finally, it is a pleasure to once more express my indebtedness to my Chief, Professor G.A. Elliott in whose department and under whose guidance the work of this thesis was carried out.

INDEX

I N T R O D U C T I O N

The quantity of iron in the body is regulated largely by the amount absorbed from the gut as the body's capacity to excrete it seems to be very limited. However three conditions have been described in which enormous amounts of iron may accumulate. Such a finding is characteristic of idiopathic haemochromatosis, it is present in a proportion of malnourished South African Bantu and is seen also in cases of refractory anaemia treated over long periods with blood transfusions.

Idiopathic haemochromatosis is a disease of unknown etiology and is associated with a characteristic clinical picture in which skin pigmentation, diabetes mellitus, hepatic cirrhosis and endocrine changes are the most prominent features. More recently heavy accumulations of iron have been shown to be present in the livers and other organs of a percentage of South African Bantu pellagrins. The histological features in some of these cases of so-called malnutritional cytosiderosis have been found to be indistinguishable from those seen in idiopathic haemochromatosis and some authors have concluded

/that ...

that chronic malnutrition initiates a derangement in intracellular metabolism which is very similar to that in idiopathic haemochromatosis. A third source of excessive iron deposition has been introduced with the widespread use of multiple blood transfusions in refractory anaemias. In some of these cases of transfusional haemosiderosis pathological findings very similar to those in idiopathic haemochromatosis have been described. A feature of several such cases has been the finding of more iron in the liver alone at autopsy than could have been present in all the blood transfusions administered. It has therefore been suggested that absorption of iron may continue to occur from the gut in spite of excessive deposits throughout the body.

The primary object of the present investigation was to study and compare the pattern of iron absorption and utilisation in these three types of iron excess. For this purpose 6 cases of idiopathic haemochromatosis, 5 cases of malnutritional cytosiderosis, 3 cases of transfusional haemosiderosis and 9 control subjects were investigated under standard conditions after each had been given a dose of radioiron by mouth. In the

/initial...

initial section of this thesis the results of this investigation are presented and their possible significance is discussed briefly.

In later sections the clinical, laboratory and pathological findings of the cases investigated are presented and an attempt is made to compare the findings in the three conditions with special reference to their possible relationship. This comparison includes an analysis of the present clinical and experimental data and of the findings and views of other workers.

C H A P T E R 1

RADIOIRON ABSORPTION STUDIES, IN IDIOPATHIC HAEMOCHROMATOSIS, MALNUTRITIONAL CYTOSIDEROSIS AND TRANSFUSIONAL HAEMOSIDEROSIS

In the following section are recorded the techniques and results of radioiron absorption studies carried out on the cases of idiopathic haemochromatosis, malnutritional cytosiderosis and transfusional haemosiderosis which were investigated in the present study. The findings in the three groups are compared with the results in a group of control subjects. The section includes a brief discussion of the results obtained in this investigation. Later sections of the thesis will include more detailed analyses of the clinical material and possible significance of the results of the radioiron absorption studies.

MATERIAL AND METHODS

The investigation was originally started in 1949 when radioiron could be obtained only from "Tracerlab", America. One case of idiopathic haemochromatosis and one control subject were studied, using this iron. Subsequently, it was possible to obtain radioiron from Harwell, England. The techniques used in the pilot study were, in certain respects, different from those employed in the other

/cases ...

cases and the dose of radioiron was larger. The results are therefore not strictly comparable with those obtained later. However, as the early results were also of some interest they have been included. To avoid confusion the pilot study is referred to as Study 1 and the later one as Study 11. The differences in technique are referred to in the relevant sections. Where no comment is made, it can be assumed that the methods were the same in the two studies.

CLINICAL MATERIAL

The 24 cases investigated are divided into 4 groups (See Table 1 and Table 11.)

/Table 1. ...

TABLE 1.

Group	Clinical Features	Sex	Age	Haemoglobin in Grams %	Total Blood Volume in ccs.	Maximum administered dose in total blood	Maximum in vivo counts over liver per min. after 1 week	% administered dose recovered in faeces
1. Idiopathic Haemochromatosis	Cardiac failure + testicular atrophy and hepatomegaly	M	21	14.5	*4500	4	275	38
IV.Control Subject.	Normal	M	± 28	16.5	*4500	0.1 (Not measured after 4th day)	0	86

* Assumed blood volume.

TABLE 11.

GROUP	CASE	CLINICAL FEATURES	SEX	AGE	HEMOGLOBIN IN GRAMS %	TOTAL BLOOD VOLUME IN ML.	MAXIMUM % OF ADMINISTERED DOSE IN TOTAL BLOOD	MAXIMUM IN VIVO LIVER COUNTS*	% ADMINISTERED DOSE RECOVERED FROM FECES
I Idiopathic hemochromatosis	1	Skin pigmentation, cardiac failure and amenorrhea	F	24	15.7	3,813	3.48	525.0	28.0
	2	Skin pigmentation, diabetes and testicular atrophy	M	37					
	1st dose				14.5	4,178	2.86	343.0	76.6
	2nd dose				14.8		3.50	160.0	79.9
	3	Skin pigmentation, diabetes and hepatomegaly	F	53					
	1st dose				12.6	4,112	1.84	170.0	76.0
	2nd dose				14.3		6.80	670.0	23.0
	4	Skin pigmentation, hepatomegaly and epistaxis	F	54					
	1st dose				14.4	3,135	1.79	75.6	92.0
	2nd dose				15.3		2.70	242.0	65.0
	5	Diabetes and hepatomegaly	F	66	13.0	4,500†	1.20	41.8	–
II Malnutritional cirrhosis	6	Skin pigmentation, diabetes and hepatomegaly	M	47	12.7	6,390	1.20	0	–
	7	Diabetes and malnutrition	F	±55	15.4	4,071	0.20	0	–
	8	Hematemesis and hepatomegaly	F	63	10.5	4,500†	0.47	0	–
	9	Diabetes and hepatomegaly	M	64	15.8	4,137	2.80	91.5	–
	10	Gross malnutrition and hepatomegaly	F	66	16.9	3,493	1.20	0	–
III Transfusional hemosiderosis	11	Lymphatic leukemia with aplastic anemia secondary to x rays. Skin pigmentation and hepatomegaly	M	44	10.1	4,500†	0.06	0	–
	12	Idiopathic refractory anemia, skin pigmentation and hepatomegaly	M	71	14.8	4,340	3.50	0	93.0
	13	Idiopathic aplastic anemia, skin pigmentation and hepatomegaly	F	49					
	1st dose				14.1	4,576	0.35	15.4	91.6
	2nd dose				9.5		0.35	24.4	91.2
IV Control subjects	14	Chronic rheumatic carditis	F	22	14.5	4,029	8.28	17.9	–
	15	Progressive bullous emphysema	M	29	15.4	5,572	4.20	0	–
	16	Diabetes	M	31	16.0	5,550	1.10	0	80.8
	17	Diabetes	F	40	16.1	5,484	7.25	0	91.6
	18	Peripheral neuritis (? infective)	M	51	15.9	4,500†	0.66	0	–
	19	Duodenal ulcer	M	56	18.8	4,013	2.99	0	79.1
	20	Diabetes	F	60	16.3	3,679	1.90	0	75.0
	21	Cirrhosis of liver and ascites	F	78	15.6	3,846	1.23	0	–

GROUP 1 - IDIOPATHIC HAEMOCHROMATOSIS - 6 Cases

Diagnosis was confirmed in all cases by liver biopsy. The patients ranged in age from 24 to 66 years. There were 4 females and 2 males. Of the females, cases 3, 4, and 5 were post menopausal while case 1, in Study 11, who was aged 24, had amenorrhoea of several years duration. All, except case 1 (Study 1), showed skin pigmentation. Cirrhosis of the liver was present in all cases but diabetes was present in only three. None had any significant anaemia. Case 3, who was diabetic, showed typical features of haemochromatosis on liver biopsy but deposits of iron elsewhere in the body were absent at subsequent autopsy except in the pancreas which showed fibrotic changes and minimal iron pigment. (Similar cases have been described by Herbut and Tamaki [17] and seem to represent a milder variant of the classical pathological picture of idiopathic haemochromatosis).

GROUP 11 - MALNUTRITIONAL CYTOSIDEROSIS - 5 Cases

These subjects, ranging in age from 47 to 66 years, all had the diagnosis confirmed on liver biopsy. Three

/were ...

were Bantu while 2 were of mixed descent. There were 3 females and 2 males. Each showed heavy hepatocellular and portal iron deposits together with portal fibrosis and bile duct proliferation. Three had diabetes, an uncommon feature in this condition (19), while the haemoglobin values varied from 10.5 to 16.9 grams % (average 14.3 grams %).

GROUP 111 - TRANSFUSIONAL HAEMOSIDEROSIS - 3 Cases

Each of these cases had received more than 100 transfusions of blood and was still receiving fortnightly transfusions at the time of the study. Two showed aplasia of the bone marrow on repeated sections of bone marrow aspirations taken from various sites at different times prior to this study. In case 12 the aplasia involved all the blood elements while in case 13 it was only affecting the red cell series. In case 12 a recent sternal puncture, taken several months after the radioiron investigation, showed a hypercellular marrow with a normoblastic reaction. The possible significance of this finding is discussed later. In the third case (No.11), the anaemia had occurred secondary to radiation therapy for chronic lymphatic leukemia, while in the other two no obvious cause for its presence could be found. In case 11,

/liver ...

liver biopsy showed heavy iron deposits in liver cells and in portal tracts, but there was no evidence of excessive fibrosis. In the other two a mild cirrhotic reaction and some bile duct hyperplasia were present and the findings were histologically indistinguishable from those found in idiopathic haemochromatosis. All these cases showed skin pigmentation but sugar tolerance was normal.

GROUP IV - CONTROL SUBJECTS - 9 cases.

All except one of these cases were selected from patients undergoing medical treatment in hospital. The remaining subject (control, Study 1) was a healthy young doctor. They ranged from 22 to 78 years and there were 5 males and 4 females. Two of the females were post-menopausal. All, except cases 14 and 21, were ambulant at the time of the study. The diagnosis in each subject in study 11 can be seen in Table 1.

PREPARATION OF RADIOIRON

The radioiron was obtained from two sources viz. "Tracerlab", United States of America (Study 1) and the Atomic Energy Research Establishment, Harwell, England (Study 11).

STUDY 1

The iron was supplied as Ferrous Sulphate with an activity, as given by the suppliers, on the date of despatch of 0.215 microcuries Fe^{59} (half life 47 days) and 0.035 microcuries Fe^{55} (half life 2.91 years) in 15 ml. solution, the total solution containing 256 mgm. Fe, i.e. 17 mg. per ml. The amount of activity administered was determined on the basis that in the first few days the whole of the radioiron would be distributed in the alimentary tract, i.e. in about 4 kg. of tissue. On this basis it was calculated that 53 μc would deliver less than tolerance (0.1 r per day). The dose actually given was 2 ml. of solution, i.e., 28 μc of Fe^{59} on the day of administration, according to the "Tracerlab" standardization. This, however, did not agree with measurements in the Council for Scientific and Industrial Research, South Africa. An absolute calibration of the radioiron gave the gamma ray activity as only 0.55 of the "Tracerlab" estimate. It seems reasonable to suppose that the radiation received by the patient was not greater than the accepted maximum permissible dose.

It was assumed that the uptake of the iron by the

/patient ...

patient and control subject, and its metabolism thereafter, would give a picture of the fate of an equal quantity (i.e. 34 mgm.) of iron in the diet.

STUDY 11

Radioactive iron was supplied by the A.E.R.E. (Harwell, England) as Fe^{59+55} derived from the Szilard-Chalmers reaction. The activities of Fe^{59} and Fe^{55} were stated to be approximately equal, in all batches obtained. Measurements in the Biophysics laboratory of the Council for Scientific and Industrial Research, South Africa, were made only of the gamma activity of Fe^{59}, by means of a high-pressure ionisation chamber, and agreed well with those made at Harwell.

Stock solutions of radioiron (ferric chloride) were prepared from these solutions. Tracer doses were then made up with activities varying from about 7 to 20 microcuries on the day of administration. Carrier iron was added to give a total quantity of 20 mgm. of iron per dose. Absorbic acid (40 mgm.) was added to each dose to reduce the ferric to ferrous iron.

/Administration...

Administration of Radioiron

All cases, except case 9 in Group 11 and the control subject in Study 1 were on routine hospital diets when the studies were done. The dose of iron labelled with radioiron was given orally 4 hours after breakfast and was diluted with water, 1 oz. of preserved fruit juice and 60 minims of dilute hydrochloric acid (B.P.). In order to trace the course of the radioiron the following measurements were then made :-

(a) Assays of all radioiron excreted in the faeces over the first seven days after administration of the iron. In study 1, urine analyses were also carried out but as the quantities eliminated were found to be very low, these measurements were not repeated in subsequent cases.

(b) In vivo measurements over various body organs up to periods of 90 days after the administration of the radioiron.

(c) Assays of radioiron in blood samples taken initially at 2 hourly intervals and at suitable periods for as long as 90 days thereafter.

/(d) ...

(d) Measurement of the radioiron content of liver biopsy material obtained 3 days after the administration of iron in case 1 (Study 1).

(e) Assays of radioactivity of organs obtained at postmortem in case 1 (Study 1).

In 3 subjects in Group 1, a second dose of radioiron was given several months after the first one. Preliminary premedication with phosphates and fat soluble vitamins was carried out prior to these second studies. Case 2 was given 120 gr. acid sodium phosphate and 60 minims haliverol, three times daily in the week preceding the administration of the radioiron and a further dose was actually given with the radioiron. Case 4 was put on a similar regime except for the use of calcium phosphate instead of acid sodium phosphate while Case 3 was given only acid sodium phosphate.

Measurements on Faeces

Where it was possible all faeces passed during the first week after radioiron administration were collected and, after digestion of the organic material, their activity was measured by means of a liquid sample

/counter...

counter of the Veall type (28). A standard solution was made up from an aliquot of the stock solution and counts made whenever a faeces sample was assayed. Direct comparison gave the activity of the faeces samples in terms of the administered dose and rendered unnecessary any correction for decay or for the changing relative activities of Fe^{55} and Fe^{59}. In Study 1 only small aliquots of the stools were taken so that the errors in measurement were relatively large.

Nursing difficulties did not allow for all faeces to be collected in some cases. Only the results of those cases in which the patients were co-operative enough to collect their own faeces are included.

It was found in Study 1, where urine analyses were also done, that the counts were not sufficiently high to allow use of a liquid counter. The iron from the urine was therefore plated using the technique described later for blood sample analyses.

/In Vivo ...

In Vivo Measurements

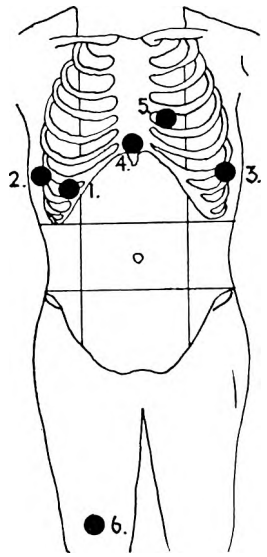

Figure 1 - Sites over which in vivo and cadaver measurements were taken.

/These ...

These were performed over several body sites (See Figure 1) with a G.E.C. end window counter (Type E.H.W. 2-Mica Window) in a lead housing. Major interest centred on the liver uptake of radioiron. In vivo measurements, except in Study 1, were started only seven days after the iron administration so as to eliminate errors introduced by the effects of the unabsorbed radioiron in the intestine on the counts over other organs. Measurements were repeated about twice weekly thereafter up to periods of as long as 90 days. It was assumed that only Fe^{59} gamma rays were being recorded as the sources being counted (e.g. liver) were at least ¾ to 1" from the counting window, this thickness of tissue being sufficient to absorb all beta rays from Fe^{59} and X-rays from Fe^{55}. No significant counts from skin or muscles could be found anywhere else on the body surface. Corrections for decay were therefore based on the half life of Fe^{59} i.e. 47 days.

Cadaver Measurements

It was soon established that high activity was concentrated over the livers of patients with idiopathic

/haemochromatosis ...

haemochromatosis. At the same time, when the Geiger-Muller counter was placed over other organs, counts considerably above background were obtained. The conditions where radioactive material is spread through a large organ of the body are not easy to imitate in vitro, and it was difficult to say how much of the count found over other organs was due to scatter from the radioiron in the liver. A model liver was therefore made up of "printer's roller composition" in which about 7 μc of radioiron had been dispersed. This model was then inserted into several cadavers where the liver had previously been removed and counts were then taken over the sites used for in vivo measurements. The ratio of counts from the source of radioactivity in the liver to those obtained over such sites was then calculated (see Table 111) so that some measure might be made as to how much counts over other organs were due to actual deposition of radioiron at these sites.

/TABLE 111 ...

TABLE 111

Site	Cadaver (Ratio, CPM/CPM over Site 1).	Patient (Ratio, CPM/CPM over Site 1).
1	1	1
2	0.92	0.96
3	0.19	0.24
4	0.53	0.45
5	0.19	0.51
6	0	0.02

Measurements on the Blood

Assays were done on the blood samples which were taken several times daily for the first few days and then at longer intervals up to periods as long as four months. The activities in the blood were determined by electroplating the sample according to a slightly modified technique of Vosburgh, Flexner and Cowie [27]. About 3 ccs. of blood were taken, weighed, dry ashed, chemically processed and plated on small copper discs in electroplating cells. The discs were then counted with a G.E.C. Counter (Type E.H.M. 2-Mica window, with a window

/thickness ..

In Vivo Measurements

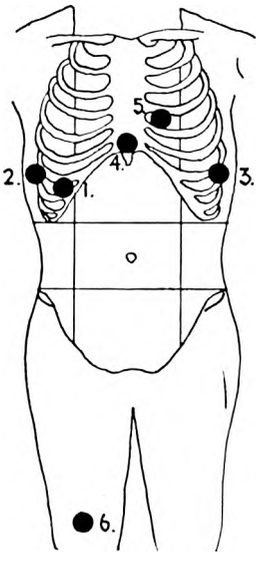

Figure 1 - Sites over which in vivo and cadaver measurements were taken.

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/TABLE III ...

TABLE 111

Site	Cadaver (Ratio, CPM/CPM over Site 1).	Patient (Ratio, CPM/CPM over Site 1).
1	1	1
2	0.92	0.96
3	0.19	0.24
4	0.53	0.45
5	0.19	0.51
6	0	0.02

Measurements on the Blood

Assays were done on the blood samples which were taken several times daily for the first few days and then at longer intervals up to periods as long as four months. The activities in the blood were determined by electroplating the sample according to a slightly modified technique of Vosburgh, Flexner and Cowie [27]. About 3 ccs. of blood were taken, weighed, dry ashed, chemically processed and plated on small copper discs in electroplating cells. The discs were then counted with a G.E.C. Counter (Type E.H.M. 2-Mica window, with a window

/thickness ..

thickness of 1.9 mgm. per square cm.) and the counts were compared with those due to plated standards made up by the same technique from aliquots of t e stock solution from which the patient's dose was derived. As with liquid sample measurements, activities of plated samples could thus be given directly in terms of the administered dose, and the p rcentage of the dose appearing in the whole blood could then be calculated. For this reason blood volumes were measured in most cases using modified Evans Blue (T1824) technique [14]. When the measurement was not made an arbitrary volume of 4,500 ccs. was assumed.

ACCURACY OF MEASUREMENTS

(a) Faeces Measurements:

Up to 10% of the faeces may have been lost in collection although it is probable that the percentage was much lower than this in most cases. The error in the chemical processing and counting procedures was found to be not more than ± 5%.

In Study 1, where only small aliquots were taken, the total error w s relatively greater and may have been as much as ± 30%.

/(b) ...

(b) Blood

Counting rates were frequently just above background and so it was necessary to count over long periods. In each determination sufficient counts were taken to reduce the error from this source to ± 5%. The error introduced by the chemical processing and electroplating procedure was estimated to be ± 4% from the spread in activities of the 6 standard plates which were used for comparison. The fluctuations in radioiron concentration in the blood were therefore determined with a probable error of ± 7%.

In the subjects who received second doses of radioiron it was not found possible to correct accurately for Fe^{55} from the first dose which may have contributed towards the counts in the second series of plated samples. The results are therefore only rough approximations.

(c) In Vivo Measurements

The counting error varied with the counting rate and with the length of the counting periods. It ranged from 10 to 26% of the counts obtained.

/RESULTS ...

R E S U L T S

Faeces Measurements: (See Tables 1 and 11)

There was a very wide individual variation in the amount of radioiron eliminated in the faeces by cases in Group 1 (idiopathic haemochromatosis) the results ranging from 23% to 92%. Unfortunately no cases in Group 11 (malnutritional cytosiderosis) could be included because of difficulties in the collection of their faeces. It is, however, probable that the percentage eliminated was high in at least 4 of these cases as they showed very low blood levels of radioiron and in vivo counts gave no evidence of organ deposition. A high percentage of radioiron was recovered from the faeces of the cases of transfusional haemosiderosis (Group 111), where figures ranging from 91 to 93% were obtained. In the 5 control subjects in whom faeces measurements were done figures ranging from 79 to 92% were recorded.

The administration of phosphates and fat soluble vitamins had no apparent effect in lowering intestinal absorption in the three cases of idiopathic haemochromatosis to whom they were given. In addition

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the presence of anaemia did not seem to increase iron absorption in Case 15, (transfusional haemosiderosis), who was given a second dose of radioiron after the haemoglobin had been allowed to fall to 9.5 grams %.

It has been assumed in all cases that the iron not excreted was absorbed into the body and not retained in gut wall as no significant counts could be shown over the gut a week after the administration of the radioiron in Groups 11, 111, and 1V. In Group 1 the low counts which were recorded could be accounted for by radioiron in the liver.

In Study 1 urine analyses were done in the 8 days after the administration of radioiron. However, the counts obtained were so low that they seemed to be of no significance (S e Table 1V).

/TABLE 1V ...

T A B L E IV

FRACTION OF ADMINISTERED DOSE IN TOTAL URINE (Study 1).

Days after Administration	Patient (Fraction, x 10^{-6})	Control (Fraction, x 10^{-6})
1st 24 hr.	317	46.1
2nd 24 hr.	28.8	3.95
3rd 24 hr.	12.2	6.2
4th 24 hr.	11.8	7.6
5th 24 hr.	4.4	12.6
6th 24 hr.	3.2	2.8
7th 24 hr.	3.1	Not measurable
8th 24 hr.	Not measurable	

In Vivo Measurements:

It was found that relatively high concentrations of radioiron were deposited in the liver in idiopathic haemochromatosis. In Study 1 the uncorrected counts per minute over this organ have been graphically represented and have been compared with those found in the control subject (see Figure 11).

/Figure 11 ...

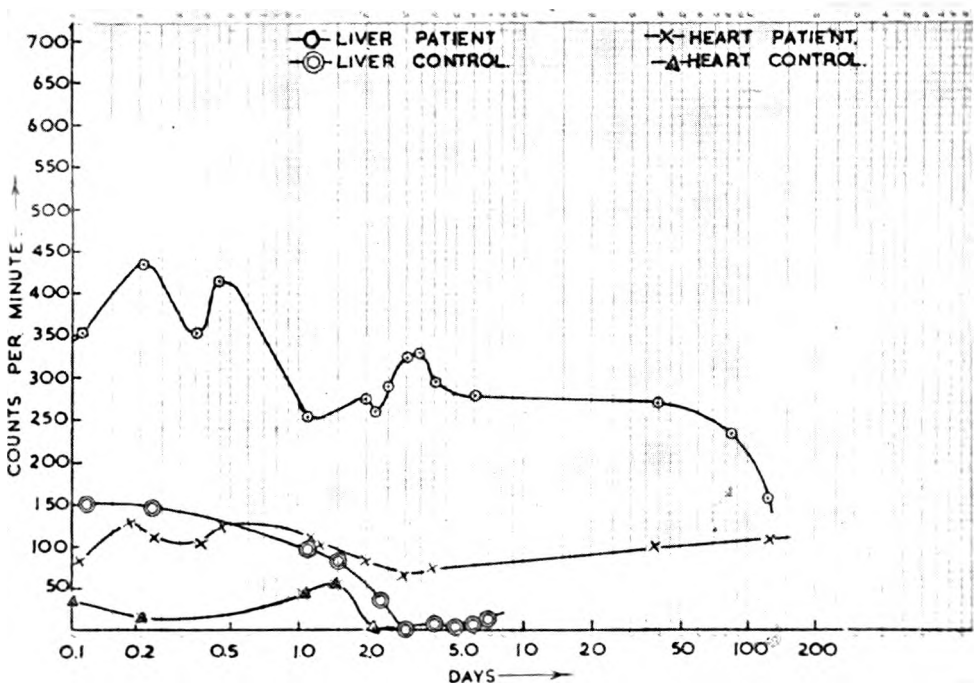

Figure 11 - Counts per minute over mid-heart and mid-liver. Case 1 (Study 1) and control (Study 1).

/The ...

The readings have been corrected for the decay of Fe^{59} (47 day half life). Although the first 7 days after administration have also been included in this graph it is doubtful whether they are valid as interfering counts, due to unabsorbed radioiron in the bowel, must have also been present. In this graph are also included counts obtained over the midheart of the patient and control.

The patient seemed to have also a real deposition of radioiron in heart muscle. The significance of this finding, in view of the patient's clinical presentation, will be discussed in a later section.

In Study 11, in vivo counts were only started one week after the giving of the iron, i.e., at a time when it could be assumed that unabsorbed radioiron in the gut had been fully eliminated. In order to be able to compare the liver counts the results were corrected to what they would have been had each subject received exactly 20 microcuries. However, differences in body build and in liver size and shape tend to make any comparison between cases a very rough one.

/The ...

The significance of counts over organs such as the liver is open to some question. It can be argued that if as much iron is leaving the liver as is entering it then the radioiron counts may still be high when the initial pool of iron in the organ is a large one e.g. idiopathic haemochromatosis, for if the radioactive and non-radioactive fractions become mixed until a state of equilibrium is reached then the iron leaving the liver should be made up of a very small radioactive fraction and a large inert one. If, on the other hand, the same amount of iron enters and leaves a liver with a low iron store, e.g. control subject, then the fraction of radioactive iron going out of the liver should be a much greater one. In the studies reported here, however, the ratio of radioiron entering the liver to the quantity of inert iron already there was low (about 1 to 500) even in the control group, where the liver iron is normally 400 to 500 mgm. [23]. If, therefore, any radioiron deposition occurred in the liver of these subjects it should have also given rise to significant counts. In actual fact, it is doubtful whether newly deposited iron is in equilibrium with the stores already present in the liver as there is suggestive evidence that the most recently absorbed iron is more readily available for utilisation than older stores [7]. On

/the ...

this basis all in vivo counts obtained over the liver a week after the administration of radioiron have been interpreted as evidence of real deposition while the absence of significant in vivo counts has been felt to represent absence of iron deposition although it is also theoretically compatible with a very rapid turn-over in the organ.

The only striking results in Study 11 were those found in Group 1 (idiopathic haemochromatosis). Every member of this group showed evidence of some organ deposition of radioiron (see Figure 111). By far the highest counts were found over the liver, although significant deposits seemed to be present in other organs such as the heart. High in vivo counts were associated with high intestinal uptakes of radioiron. In 4 of the 5 subjects with malnutritional cytosiderosis (Group 11) no evidence of organ deposition of radioiron was found. In the remaining case (No. 9) significant, though not very high counts were obtained over the liver. The results have been graphed in Figure 111.

/ FIGURE ...

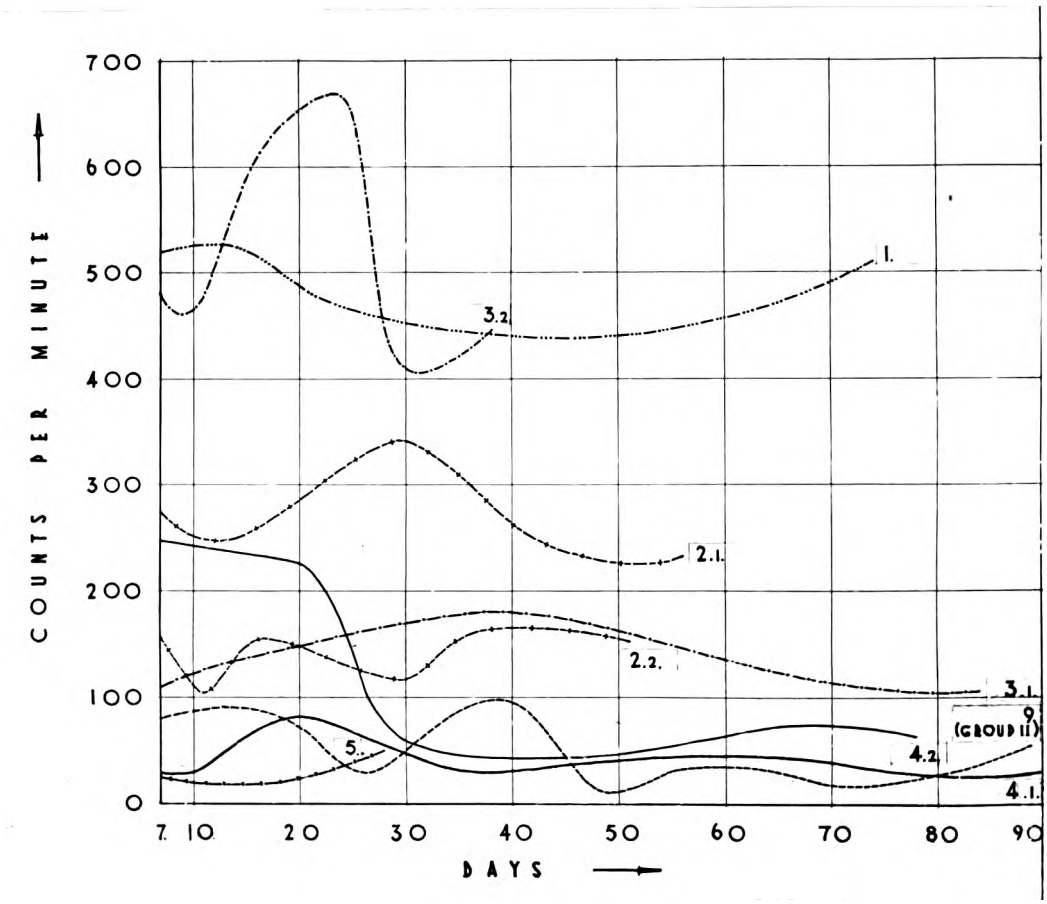

FIGURE 111 - Showing the in vivo counts over the livers of subjects in Group 1 (idiopathic haemochromatosis) and of case 9 in Group 11 (malnutritional cytosiderosis.

There was no evidence of any uptake of radioiron in 2 of the 3 patients in Group 111 and in 7 of the 8 subjects in Group 1V. In one of the cases with transfusional haemosiderosis (case 13) and in one of the control group (case 14) very low liver counts were recorded on several occasions. Case 14 had hepatomegaly secondary to previous bouts of congestive cardiac failure. The importance of her low, but probably significant, deposition of radioiron in the liver is not apparent but may have been related to hepatic congestion. It was accompanied by a very high blood uptake (8.28%) and requires further study.

Blood Uptake:

The results are resented graphically as the percentage of the administered blood in total blood. In a few cases accurate figures for blood volume were not available; in such circumstances an arbitrary blood volume of 4,500 ccs. was used. The error of this assumption is not a large one.

In case 1, Study 1, the results are presented logarithmically in order to bring out the initial peak which occurred at about three hours after the administration of the iron (see Figure 1V).

/FIGURE 1V ...

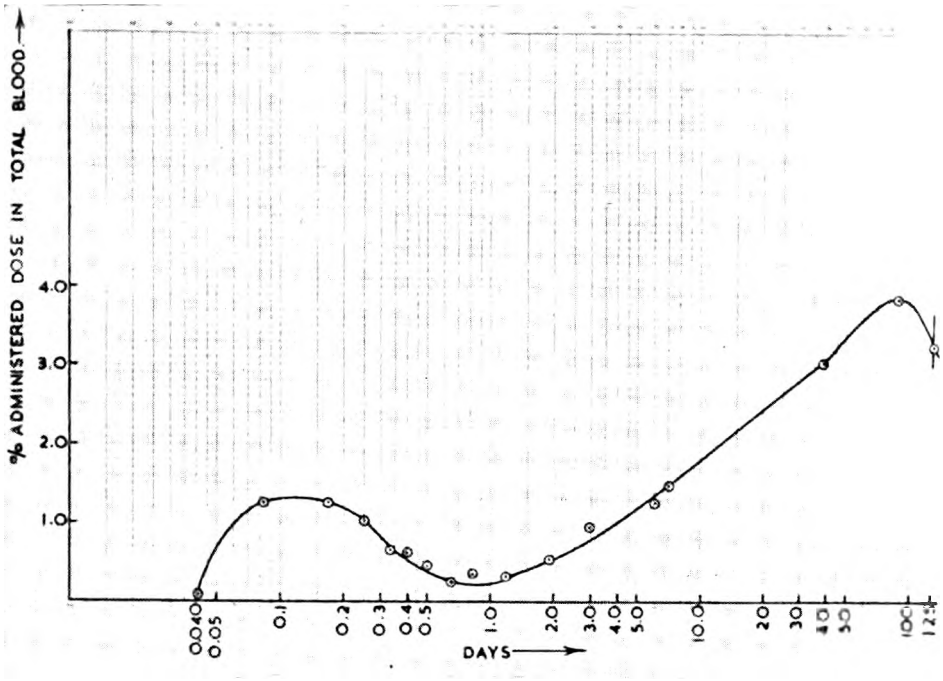

Figure 1V - Uptake of radioiron in the blood of Case 1 (Study 1).

/It ...

It is presumed that this peak represents the initial uptake of iron in the plasma. The drop in radioiron in the blood and subsequent rise shows how the iron was removed from the plasma, stored, and gradually built into the haemoglobin until after three months something of the order of 4 per cent of the total administered iron was found in the red blood cells. In the sample taken on the sixth day (10 c.c.) the cells were centrifuged off, and all the radioiron was found to be in the cells; there was none in the plasma. In the control subject (Study 1) no measurable amount of radioiron was found in any of the blood specimens taken until the third day. On the third and fourth days after measurement something of the order of 0.1 per cent of the administered dose per 4,500 ml. of blood was found. This was barely measurable (1/1,500 of 0.1 per cent in 3 ml. blood). No further blood specimens were

/taken ...

taken. Subsequently it was found in other cases that significant levels of radioiron may appear in the blood at later periods and it is felt that sampling was stopped too soon in this subject. Too much stress can therefore not be put on the low blood levels recorded in this case.

In Study 11 the initial uptake within the first few hours was again found to be in the plasma. Thereafter, a slow buildup in the haemoglobin occurred over several days and this level was then roughly maintained for periods up to 120 days. The results for each group have been graphically represented but an ordinary time scale has been used so that the original plasma peak is not shown.(see Figures V - IX).

/FIGURE V ...

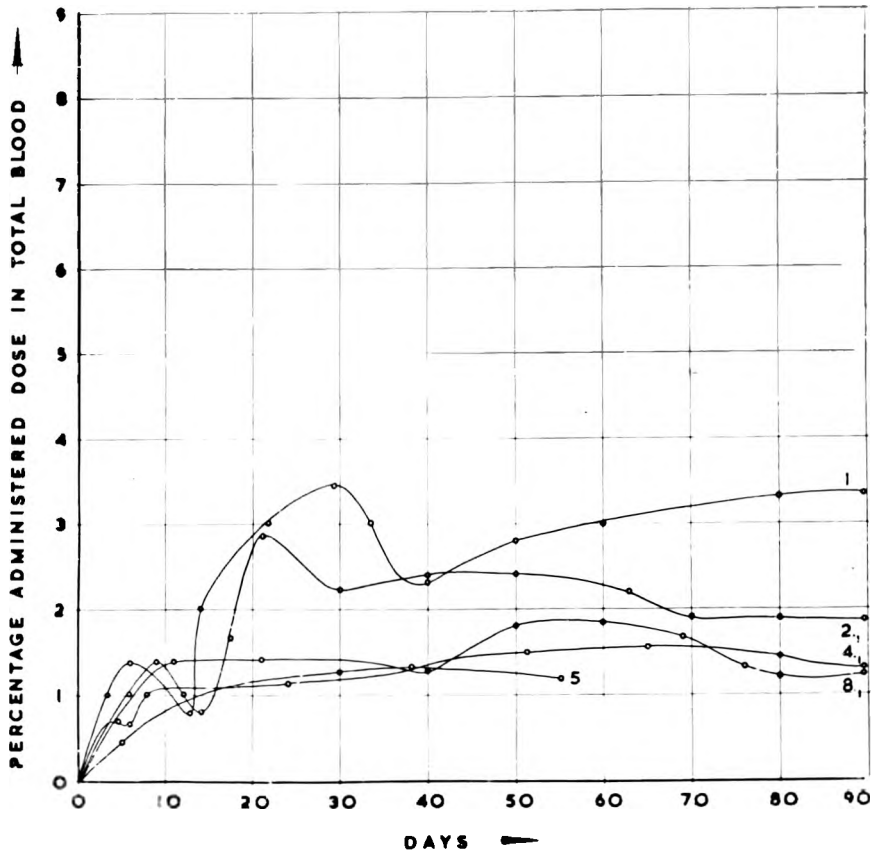

FIGURE V - Showing the blood uptake in Group 1, (idiopathic haemochromatosis).

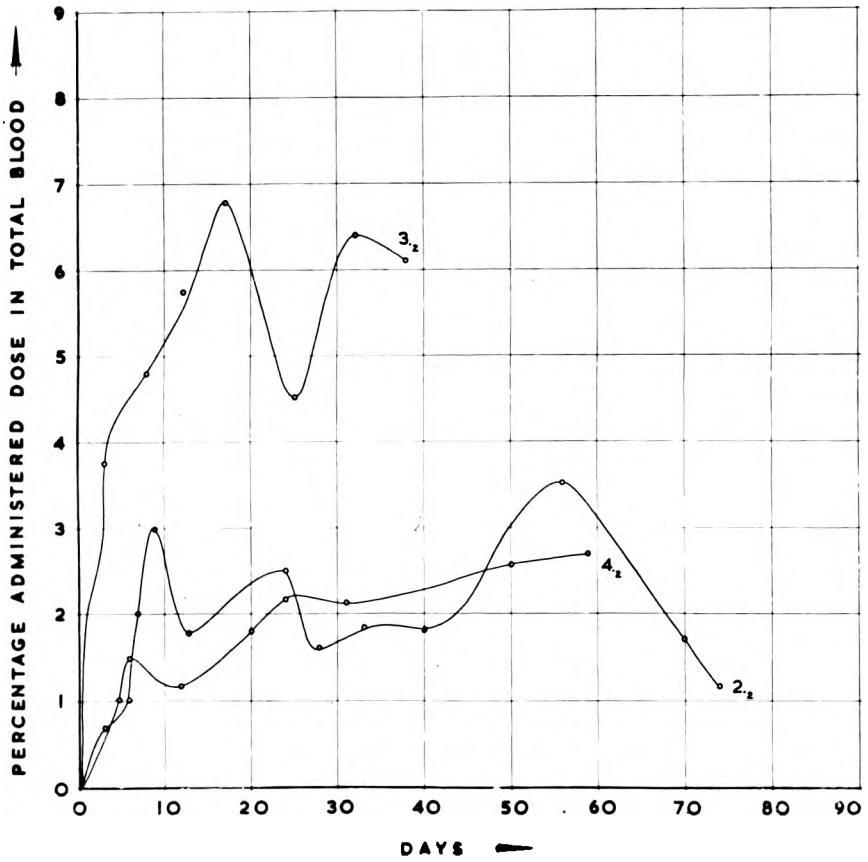

FIGURE V1 - Showing the blood uptake in Group 1 after the administration of fat-soluble vitamins and phosphate mixtures.

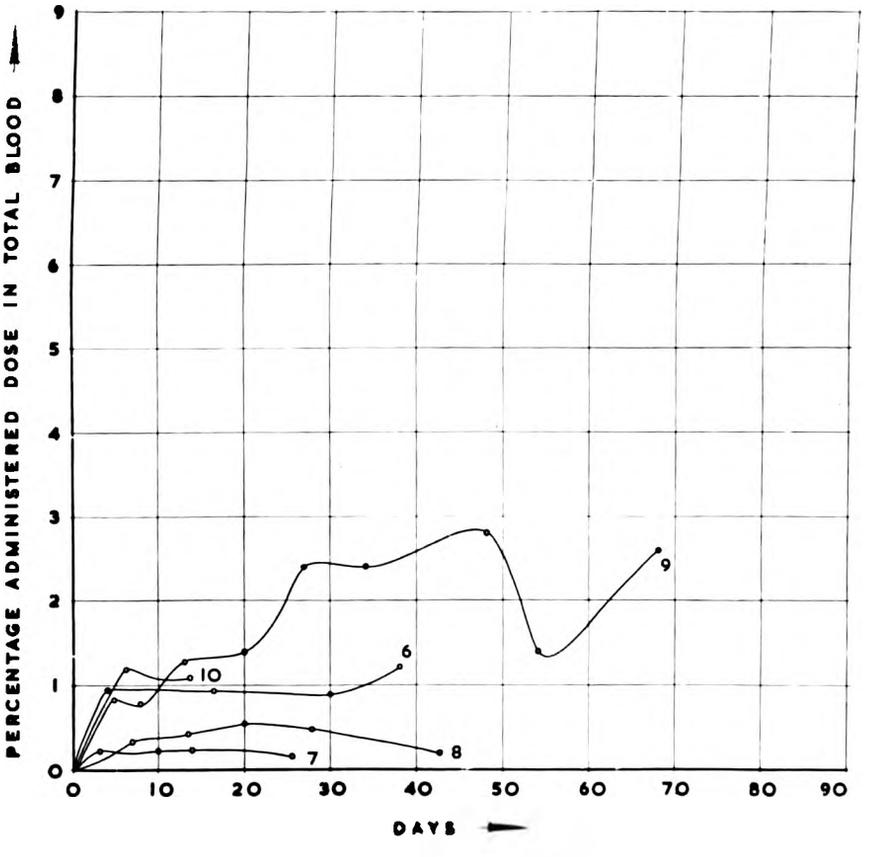

FIGURE V11 - Showing the blood uptake in Group 11 (malnutritional cytosiderosis).

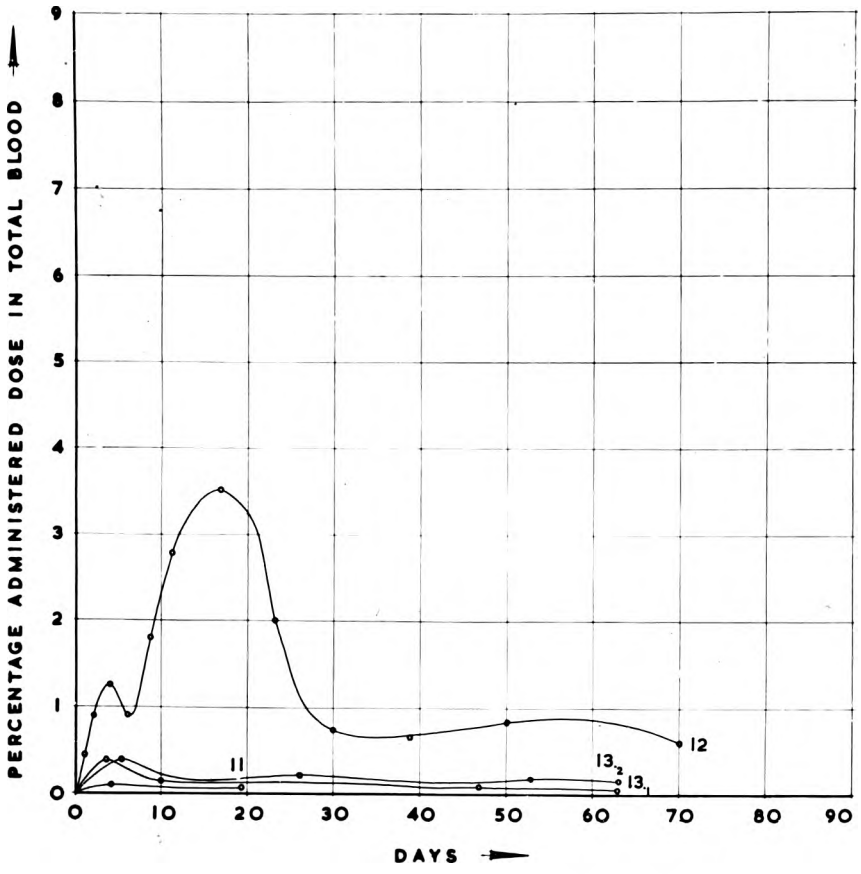

FIGURE V111 - Showing the blood uptake in Group 111 (transfusional haemosiderosis.

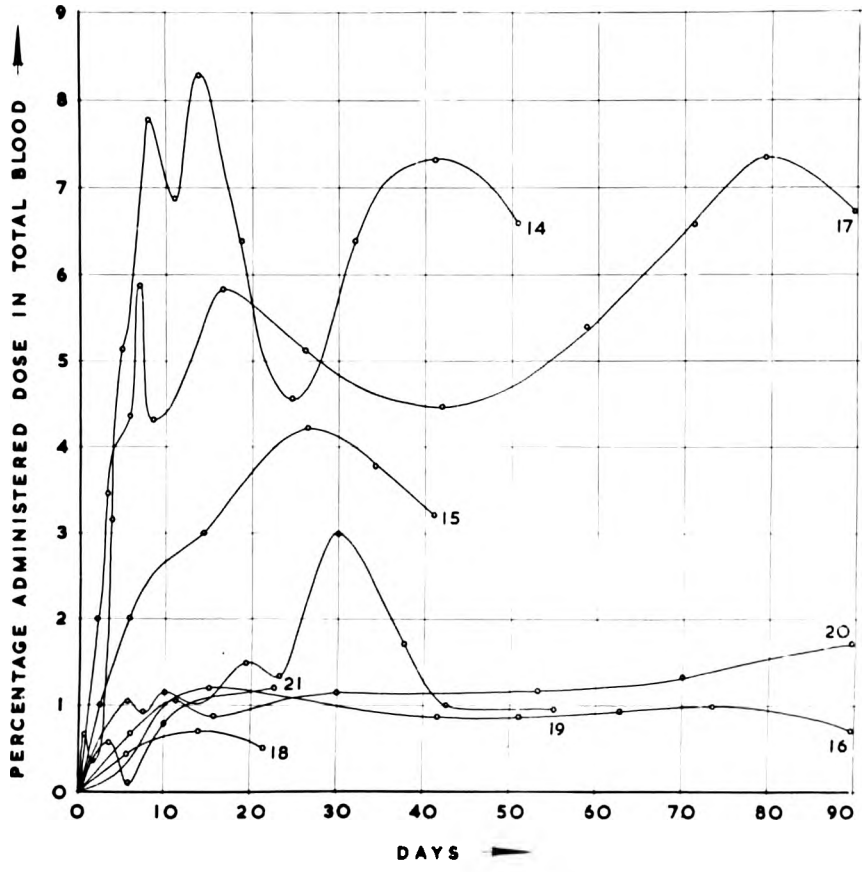

FIGURE 1X - Showing the blood uptake in Group 1V, (control subjects).

There was a wide variation in the maximum blood uptake in Group 1 with a range of 1.8 to 6.8% (see Figure V). The administration of fat soluble vitamins and phosphate mixtures in 3 cases in this group did not seem to affect the degree of absorption (see Figure Vl). In Group 11 the maximum blood uptake was low, ranging from 0.2 to 2.8% of the administered dose (see Figure Vll). The results in transfusional haemosiderosis can be seen in Figure Vlll. In two cases (No. 11 and 13) the blood uptake was very low (.06 and .35%). In one of these (No. 13) the study was repeated when the patient was anaemic (Haemoglobin 9.5 G.%) but similar results were obtained. The third case (No. 12) is of special interest as he showed a significant level of 3.5% of the administered dose in spite of the fact that repeated bone marrow punctures had shown an aplasia of the marrow. Another feature was the unusually short period that the radioiron was maintained in the blood at its maximum level, falling from 3.5% to 0.7% of the administered dose between the 15th and 30th days.
In view of these results a further bone marrow aspiration

/was ...

was performed subsequent to the radioiron investigation. On this occasion the marrow was hypercellular and showed a normoblastic reaction. It therefore seems probable that case 12 was forming blood in a normal way at the time of the radioiron investigation in spite of the previous evidence of marrow aplasia. In addition the rapid fall in the blood level of radioiron between the 15th and 30th days suggests that blood destruction was occurring at an increased rate. Evidence of haemolysis, as judged by a raised serum bilirubin, increased urinary urobilin and reticulocytosis was, however, lacking. The appearance of radioiron in the blood of case 12 seemed to show that iron absorption may continue to occur in spite of heavy body stores of iron and in spite of an almost saturated serum iron level (Serum iron 211 micrograms %; total iron binding capacity 2 5 micrograms%). The individual variation in maximum blood levels was wide in the control subjects (Group IV) with a range from 0.66 to 8.8% (see Figure IX).

A composite graph is included to aid in comparison (see Figure X).

/FIGURE X ...

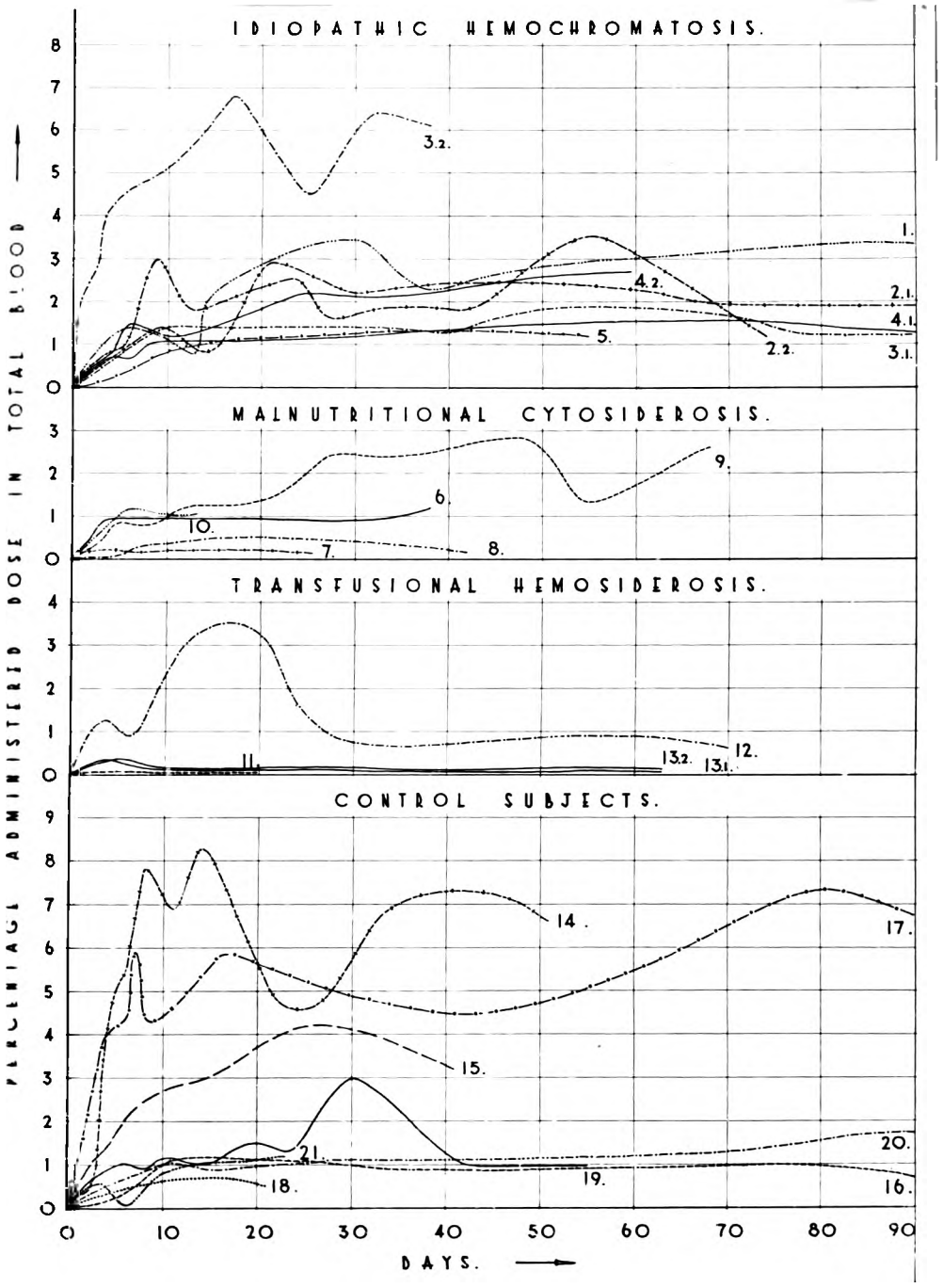

FIGURE X - Showing a composite graph of the blood uptake in each group.

Liver Biopsy Measurements:

The biopsy was performed on Case 1 (Study1) three days after the administration of radioiron. The total dry weight of material received was about 3 milligrams. The sample when plated gave a net count of 11 cpm, the standards on the same day counting 1,160 cpm. Thus 5.2×10^{-4} of the total dose was found in the liver, per gram of dry weight or about 1.0×10^{-4} of the total dose per gram of fresh weight. It is of interest to compare this with the result of the assay on the liver made after postmortem (see postmortem measurements), when the count was 1,830 cpm per gram dry weight, the standards giving at that time a count of 543 cpm. The fraction of total dose per gram dry weight of tissue was therefore 5.3×10^{-4}. In view of the large probable error involved both in weighing and in working with only 3 mg. of material, the agreement is satisfactory, but the accuracy of the measurements is not sufficient to warrant any inference being drawn as to increase or decrease with time of the amount of radioiron in the liver.

Postmortem Measurements:

Case 1 (Study 1) died several months after the administration of radioiron. Unfortunately it was not

/possible ..

possible to obtain all the organs but radioactive assays were made on those which were available. The results are presented in Table V.

TABLE V.

Tissue	Fraction of Dose per Gm. Dry Wt. x 10^{-4}	% Iron (Stable) found in organ.
Liver	5.32	0.726
Pancreatic lymph glands	2.64	0.371
Kidney	2.24	-
Mesenteric lymph glands	1.43	0.080
Pancreas	0.496	0.313
Spleen	0.362	-
Duodenum	0.249	0.0767
Pyloric end of stomach	0.126	-
Mass of mesentery lymph glands.	0.052	-

It can be seen that the greatest amount of radioactivity was present in the liver. Unfortunately with no knowledge of the total liver weight it is not possible to say what total amount of radioiron was stored in this organ. If one could assume the liver to have been of normal weight, viz. about 1.6 kilograms, one could say that some 15 to 20 per cent of the administered dose had been stored in the liver. It is known that the patient's liver was in fact considerably

/enlarged...

enlarged; the percentage of administered radioiron stored in the liver might therefore easily have been as high as 30 per cent.

D I S C U S S I O N

The value of the tracer technique in studying iron absorption has been shown by several studies (6), (8), (15). It seems that the method may be more accurate than earlier chemical iron balance studies where difficulties may arise due to the presence of phosphorous-iron compounds (1). However, the radioiron method is itself open to misinterpretations as it is impossible to obtain a complete reflection of iron absorption patterns with only a single dose of labelled iron. In addition Dubach and co-workers (9) recently showed that earlier results in radioiron absorption studies are partly invalidated by their assumption that the quantity of radioiron circulating in the blood was equal to the amount absorbed. Dubach, therefore extended the technique to include assessments of the quantities of unabsorbed radioiron present in faeces and was able to show suggestive evidence that

/normal ...

normal and abnormal subjects may absorb more iron than they immediately utilise for haemoglobin formation.

In the present study Dubach's method was extended to include in vivo counts over various body sites. With this technique it was possible to exhibit a pattern of radioiron utilisation in idiopathic haemochromatosis which was constant enough to be of diagnostic value. Previous absorption studies in this disease have given conflicting results. Chemical iron balance investigations have shown an abnormal retention in only two cases [9], [20] while no abnormality could be detected in several others [6], [9]. Tracer iron studies have also given conflicting results as Balfour and co-workers [1] could show no evidence of increased iron absorption in a case investigated by them on two occasions while Dubach and co-workers [11] showed a significant absorption in another. It is possible that the apparently low uptake in Balfour's patient was due to the fact that only blood measurements were done.

In the present study there was a tendency for a greater uptake of iron to occur in idiopathic haemochromatosis as compared with the control and other groups. In three cases, (No. 1, Study 1 and 11 and No. 3 (2nd dose)) this was strikingly so. It is of

/interest ...

interest that in the only two young subjects with idiopathic haemochromatosis investigated (case 1 in Study 1 and case 1 in Study 11) very high figures for absorption of radioiron were obtained. This finding offers a possible explanation for the poor prognosis in younger subjects (see later section). It is also possible that the cardiac damage so frequently found in these patients may be due to the insult of the increased rate of deposition of iron in cardiac muscle which occurs secondary to the high intestinal absorption. This contention will be discussed in more detail in a later section. Blood and in vivo counts in the cases of idiopathic haemochromatosis showed that a proportion of the absorbed iron was utilised for haemoglobin formation and that the remainder was deposited in the liver and other organs. The range of blood uptake in this disease was very similar to that in the control group (1.84 to 6.8% as compared with 0.66 to 8.8%). However, as the excretion of radioiron in faeces was less in at least some of the cases of idiopathic haemochromatosis and as significant organ deposits were present in all cases it seems probable that the actual percentage of absorbed iron utilised for haemoglobin formation was lower than normal. This observation agrees with Finch and co-workers finding of a low

/percentage . . .

percentage utilisation of intravenously administered iron in this disease [1].

Experimental evidence has suggested that dietary factors may play a part in regulating iron absorption. Increased absorption has been produced in depancreatised cats [24], in cats after ligation of the pancreatic ducts [25] and in rats fed on an iron supplemented corn grit diet.[19]. This increased absorption could be partially prevented in the cats by the addition of haliverol to the diet [25] and in rats by the addition of phosphate [19]. On this basis Granick [13] has suggested that such measures deserve trial in idiopathic haemochromatosis in spite of the lack of evidence of undernutrition as an etiological feature. Three of the present subjects were therefore given various phosphate-haliverol mixture in large doses prior to the administration of a second dose of radioiron, several months after the first one. The results showed no evidence of any blocking of iron absorption. Indeed the blood uptakes and in vivo counts on the whole were higher in the second study. The findings in this second study also seem to show that the rate of iron absorption in idiopathic haemochromatosis varies from time to time in the same individual although the pattern of high intestinal

/absorption ...

absorption, heavy organ deposition and a relatively low haemoglobin utilisation is constant.

Results in malnutritional cytosiderosis were conflicting. The average uptake in blood was low. The total uptake of iron from the gut is not known because of difficulties in faecal collection. However, it was probably very low as the percentage in the blood was low and there was no evidence of any significant organ deposits. The re aining subject (case 9) is of interest as he was the only one studied while still on the "Kaffir" beer and maize porridge which forms the basis of the avera e South African Bantu diet. His blood uptake was 2.8% and he showed a significant deposition of radioiron in the liver (see Figure Vll). Controversy exists as to whether the malnutritional cytosiderosis described by the Gillmans (11), (12), is indeed a disease entity as recent pathological studies have shown striking difference between it and idiopathic haemochromatosis. High concentrations of iron have been shown in the spleen while little or no iron has been found in the heart or pancreas (13). It has been

/suggested ...

suggested [18] that the high quantities of iron in South African Bantu diets (as much as 200 mgm. daily [29]) allow for greater absorption but that this is not necessarily pathological as Hahn's "mucosal block" has been shown to be only a relative one [1?]. However, case 9 seemed to absorb a significant percentage of the small dose of 20 mgm. radioiron and to deposit a proportion of it in the liver in an abnormal fashion. The low absorption in the other 4 subjects was possibly related to the fact that they had been on normal hospital diets for some time prior to the study. However, this is pure speculation and the role of such deficiencies as phosphates, fat soluble vitamins and pyridoxine in influencing iron absorption in this condition requires further tracer studies.

There was, on the whole, a low uptake of radioiron in transfusional haemosiderosis. Faeces measurements suggested that about 10% of the dose was retained and only a small proportion of this was utilised for haemoglobin formation in two of the cases. A haemoglobin uptake of 3.5% was present in one subject (case 12). This finding is of importance in so far as it shows that iron may continue to be absorbed in this condition in spite of enormous body iron stores. It thus offers

/a possible ...

a possible explanation for the previously unexplained autopsy finding of more iron in the livers of some cases of transfusion haemosiderosis than was present in all the blood transfusions which they had received. (21), (30), (31). In one subject (case 13) counts above background were obtained over the liver on both occasions on which she was investigated. This finding suggests that some iron which had been absorbed was being stored in the liver. The presence of anaemia did not influence the degree of iron absorption in this case.

The figures for iron absorption and utilisation in the control subjects were more or less similar to those found by Dubach and co-workers in normal cases (4) although their figures for blood uptake were greater than ours in spite of the fact that they gave ± 3 times the dose which we used. This may have been partly due to the fact that all except one of our cases were suffering from some form of disease (see Table 11). Dubach noted a wide individual variation in blood uptake under standard conditions and this was also a feature of the present study where a range of 0.66 to 8.28% of the administered dose was found in the blood. Suggestive

/evidence...

evidence was obtained that some of the radioiron taken up by the body was not being utilised immediately for haemoglobin formation in the 4 control subjects who had faeces analyses done. An average of 18.4% was retained while only 3.31% appeared in the blood. Although too much significance cannot be attached to these results because of inaccuracies in faeces measurements, similar findings have been reported by Dubach and co-workers (9).

S U M M A R Y & C O N C L U S I O N S.

(1) The pattern of radioiron absorption was studied in idiopathic haemochromatosis, malnutritional cytosiderosis, and transfusional haemosiderosis and the results were compared with a group of control subjects. The passage of the iron was followed by faeces analyses, (except in malnutritional cytosiderosis) multiple blood sampling and in vivo measurements.

(2) Increased iron absorption was found in idiopathic haemochromatosis. A proportion of the absorbed iron was utilised for haemoglobin formation and the remainder was deposited in the liver and other organs. Neither phosphates nor fat soluble vitamins were found to influence the rate or pattern of absorption.

(3) The absorption of iron from the ut seemed low in 4 cases of malnutritional cytosiderosis. In the remaining one a significant blood uptake and an abnormal deposition in the liver were found.

(4) Iron absorption was not completely absent in transfusional haemosiderosis, although haemoglobin utilisation was very low in all except one subject. It would seem that absorption of iron may continue to occur in this condition in spite of saturated body iron stores.

/There ...

(5) There was a wide individual variation in the level of radioiron in the haemoglobin of the control subjects and suggestive evidence that all the absorbed iron was not necessarily being immediately utilised for haemoglobin formation.

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C H A P T E R 11.

IDIOPATHIC HAEMOCHROMATOSIS.

Idiopathic haemochromatosis is a disease of unknown etiology, which is associated with the slow accumulation of iron in the body. The condition is found predominantly in males (95%) and occurs usually between the ages of 35 and 50 years. (2). The presenting complaints may be related to skin pigmentation, diabetes, endocrine hypofunction and heart failure. The frequency of these features varies. Sheldon (2) found that hepatic cirrhosis was present in all cases, diabetes was present in 78% and pigmentation of the skin was seen in at least 80%. Evidence of endocrine dysfunction, such as testicular atrophy with impotence, is less common while features of cardiac failure are rare except in younger subjects (10), (11), (12).

At autopsy the total iron in the tissues has been estimated at 25-50 grams compared with the normal maximum of 5 grams. Pathologically the diagnostic feature is the deposition of iron in the form of haemosiderin in the liver, the heart and throughout the landular tissue of the body, including stomach glands, salivary glands and sweat glands. There is an associated fibrosis in the liver and pancreas and to

/a lesser ...

a lesser extent in other organs. In addition, there are deposits of haemofuscin, an iron free pigment related to melanin, especially in smooth muscle. A feature of idiopathic haemochromatosis is the relatively low concentration of iron to be found in the spleen, kidneys, and bone marrow which is in marked contrast to the findings in the haemosiderosis found after long continued haemolysis (72). Although the clinical and pathological findings in idiopathic haemochromatosis have been well described, little is known of its underlying cause. It has been regarded up to the present as an inborn error in metabolism of unknown etiology associated with the slow accumulation of iron in the body over many years.

In the section which follows, clinical details are presented of the cases with idiopathic haemochromatosis in whom radioiron studies were done. Aspects of the disease are discussed with special reference to the findings in the present investigation. The subject as a whole is not reviewed in great detail as this has been done comprehensively by others (4), (56), (72). The results of the present study did, however, throw some light on the nature of the metabolic defect in the disease and on the possible pathogenesis of cardiac complications. These aspects are therefore discussed

/at more ...

at more length.

CLINICAL MATERIAL (GROUP 1).

CASE 1. (Study 1) a prison warder, aged 21 years was admitted to the Johannesburg General Hospital in September, 1948 with a history of several bouts of palpitations. During the night of 10th September, 1948, he was woken by 'palpitations'. The heart was rapid and the beat seemed regular. After half an hour the attack came to an end, the heart suddenly returning to its normal rate. During the night he had, in all, five such attacks. By the morning he was well again. He was referred, however, to the Out-Patient Department of the hospital for electrocardiographic studies. Because of the electrocardiographic findings he was admitted to the hospital eight days after the initial attack.

Previous exercise tolerance was good and there was no history of rheumatic fever, growing pains or recurrent sore throats. Appetite was good and he had always been on a well-balanced nutritious diet. He neither drank nor smoked, and the family history was not contributory.

/Physical ...

Physical Findings on Admission. He was a well-developed young adult male weighing 143 lbs., and 5'9" tall. He was aprexial. He looked younger than his stated age because of an almost complete absence of facial hair. Both axilliary and pubic hair were scanty, the pubic hair having a female distribution. His colour was good, and there was no abnormal skin pigmentation. There was no breathlessness at rest.

When lying at an angle of 45° he had pulsatile neck veins 3-4 cm. above the angle of Louis. The pulse rate was 84 per minute and was irregular due to extra-systoles. The blood pressure was 90/60 mm.Hg. Clinically the heart was normal in size. On auscultation, a gallop rhythm was heard at the apex. The liver was felt two fingers below the costal margin, the edge being very firm, smooth and not tender. The spleen was not felt. The size of the penis was within normal limits but the testicles were markedly atrophic. No other features were found on general examination.

It was felt that some form of myocarditis was present and he was investigated from this point of view.

/Laboratory ...

Laboratory Data. Full blood count: Haemoglobin 14.5g %., erythrocytes (per c.mm) 4,920,000., leucocytes (per c.mm) 11,000., neutrophils 68%., monocytes 4.5%., lymphocytes 24.5%., eosinophils 3.0%., basophils 0., Sedimentation rate: slight increase., Antifibrinolysin Titre ++++ positive. Modified Ide Test for Syphilis: negative, Nasal and throat swabs: negative for C. diptheriae. Urine: chemically and microscopically negative. X-ray of the chest showed the heart to be within the normal limits of size, shape and position, the transverse diameter being 5½". The lung fields were clear. Electrocardiographic findings: rate, 84 beats per minute. There was a constant reduction in amplitude in leads 1-111 PR and QRS times were within normal limits. The chest leads CR 1-6 were characterized by large inverted T waves in positions 1-4. In position 5 and 6 the T waves were practically iso-electric. Ventricular extrasystoles, multifocal in origin, were present in all records taken. Weekly electrocardiographic tracings showed no change in the basic pattern. Ballistocardiograms: Both high frequency (Starr et al. (32)) and low frequency tracings, gave a stroke volume of 54.6 c.c. and a cardiac output of 4.8 litres per minute. (Normal range 4-8 litres per minute). The stroke volume was at the lower limits of

/normal ...

normal.

Clinically he remained asymptomatic. In view of the persistent, non-tender hepatic enlargement, a set of liver function tests was done, but with negative results. However, a liver aspiration biopsy showed evidence, on microscopic section of advanced haemochromatosis, with heavy iron deposits. In view of this finding additional laboratory tests were carried out.

Additional Laboratory Data: Sugar tolerance curves (after 50 grams glucose orally) gave the following results (Blood sugar values in mg. per 100 c.c.):-

Date.	Fasting.	30 Minutes.	60 Minutes.	90 Minutes	120 Mins.
28 October, 1948.	100	210	220	155	135
16 March 1949	90	165	135	--	95

On duodenal intubation pancreatic ferments were found in normal amounts. Adrenal function seemed adequate as judged by a normal blood sodium and a negative Robinson-Kepler-Power test. Basal metabolic rates on three occasions gave results of -35%, - 17%, and -25%.

He was discharged from hospital on 21st December,

/1948 ...

1948 there having been no significant change in his condition. He was re-admitted on 1st January, 1949 with a week's history of attacks of palpitations, similar to those described on his previous admission. There was no change in the physical and laboratory findings. On the second day after admission he complained of sudden breathlessness and on examination it was found that he was having paroxysmal bursts of tachycardia which were shown on electrocardiography to be ventricular in origin. He was given quinidine sulphate and within three hours the rhythm returned to normal. In the next few days he had two more attacks of paroxysmal tachycardia. The patient was well enough to be discharged on 5th February, 1949.

On May 7th, 1949, he was again readmitted with a two-week history of increasing breathlessness on exertion and of palpitations. On examination it was found that he was in congestive cardiac failure. Radiological examination showed slight cardiac enlargement, more marked in the left than in the right ventricle. He was treated by bed rest, a salt free diet and digitalis leaf. All signs of congestive cardiac failure had disappeared after a week, and he was discharged. When the patient was last seen alive on 3rd July, 1949, he was still able to carry out light duties.

/However ...

However, on 8th August, 1949, he collapsed in the street and died before admission to hospital.

A post-mortem examination was carried out by a pathologist unaware of the patient's history. The diagnosis of idiopathic haemochromatosis was confirmed. Microscopically there was dark brownish pigmentation of the liver and mesenteric glands and the pancreas was represented by a thin fibrous cord. Histologically both organs showed heavy iron deposits. In addition, there was an early portal fibrosis in the liver and, in the pancreas, there were thick bands of connective tissue running between the acini. The heart also showed brownish discolouration and there was a slight generalized enlargement (16 oz.). However, no sections were made, so that the histological features are not known.

CASE 1 (Study 11):- a widow aged 22 years, was admitted to the Johannesburg General Hospital on February 6th, 1950, complaining of amenorrhea for twenty months. Previous health had been good, and she had given birth to a normal baby in 1946. Six months after the onset of the amenorrhoea, the skin began to darken. Both family and systemic histories were non-contributory.

/On Physical ...

On Physical Examination she was well developed. A generalized slaty gray skin pigmentation was found, and both axillary and pubic hair were scanty. A bigeminal rhythm accounted for a pulse rate of 44 per minute, which was one-half the rate counted over the heart. The blood pressure was 126/70 mm.Hg. and there was no clinical cardiomegaly or abnormality of the heart sounds. The liver edge was just palpable, being firm and non-tender. Gynecological examination proved negative.

Progress: She was asymptomatic in the hospital. She had frequent extrasystoles, but these caused no subjective disability. The patient was discharged, with no definite diagnosis, on February 27th, 1950.

Laboratory Data: A complete blood count showed the following: haemoglobin 13.8 gm.%, erythrocytes (per cubic millimeter) 4,650,000, leucocytes (per cubic millimeter,) 10,000, neutrophils, 41.0%, monocytes 11.0%, lymphocytes 44.5%, eosinophils, 3.5%, basophils 0%. Blood proteins; albumin 2.5 mg.%, globulin 3.9 mg.%. Serum sodium 344 mg.%, serum sodium chloride 560 mg. %, blood urea nitrogen 38 mg.%. Sugar tolerance curve (after 50 gm. of glucose by mouth) fasting level 100 mg.%, 15 minutes 105 mg.%, 30 minutes

/110 mg.% ...

110 mg.%, 60 minutes 150 mg.%, 120 minutes 120 mg.%, 180 minutes 105 mg.%. Liver function: Thymol turbidity test, 3.5 units, thymol flocculation, negative, cephalin cholesterol flocculation (twenty-four hour reading), +++ positive, Takata-Ara (Ueko's modification) ± positive. Prothrombin index 83%. Modified Ide test for Syphilis: negative. Urine analysis was normal. A Kepler-Robinson-Power test was positive. A skin biopsy was negative. An electrocardiogram on February 8th, 1950 showed inconstant bigeminal rhythm due to alternating ventricular extrasystoles. The rate was 80 per minute. Basic rhythm showed a flat T wave in Lead V_6 and diphasic (+ -) T waves in V_4 and V_5 (Figure 1). There were runs of ventricular extrasystoles up to six beats. On February 21st, 1950, the inconstant bigeminal rhythm was still present. X-rays of the heart, lungs, and skeleton were normal.

Second Admission: The patient had been well until four days before readmission on March 28th, 1951, when she developed short bouts of 'palpitations' with a rapid, regular heart rate. During one such attack, she became extremely breathless and lost consciousness for a few moments.

/On Physical ...

On Physical Examination: There was generalized skin pigmentation and marked orthopnoea. The pulse rate was ± 170 per minute, the rhythm was irregular, and the blood pressure was 80/55 mm.Hg. She was in congestive cardiac failure and peripheral circulatory failure with a cold clammy skin. The neck veins were engorged and pulsatile at an angle of 45°. The heart was not clinically enlarged, and the sounds were normal. The liver was enlarged 3 finger-breadths, and the edge was smooth and tender. There was no peripheral oedema.

Progress: Digoxin, 0.5 mg., was injected intravenously, and the condition improved dramatically. After two hours, the pulse was regular with a rate of 96 per minute, and the blood pressure rose to 110/65 mm.Hg. Maintenance therapy was continued with 0.25 mg. of digoxin twice daily and with 6 gr. of quinidine sulphate four times daily. After several days there were no signs of congestive failure, and the heart was regular except for occasional extrasystoles. While the patient was in hospital, the diagnosis of idiopathic haemochromatosis was established by liver aspiration biopsy. She was discharged on April, 21st, 1951.

/Laboratory ...

Laboratory Data: A complete blood count showed the following: Haemoglobin 15.7 gm.%, erythrocytes (per cubic millimeter), 5,000,000, Leucocytes (per cubic millimeter) 8,900, neutrophils 46.0%, monocytes 7.0%, lymphocytes 44.5%, eosinophils 0.5%, basophils 2.0%, Blood proteins: albumin 3.8 gm.% globulin 3.9 gm.%. Serum sodium 337 mg.%, Serum sodium chloride 550 mg.%, serum potassium 20 mg.%, phosphorus 4.8 mg.%, calcium 10.6 mg.%, cholesterol 195 mg.%, amylase 74 units. Sugar tolerance curve (after 50 gm. of glucose by mouth): fasting level, 70 mg.%, 30 minutes 78 mg.%, 60 minutes 110 mg.%, 90 minutes 70 mg.%, 180 minutes 60 mg.%. Liver function tests: Thymol turbidity test ++ positive, cephalin cholesterol flocculation negative, Takata-Ara (Ueko's modification), negative, van den Bergh reaction negative, bilirubin, direct, less than 0.5 mg.%, total less than 0.5 mg.%, Icteric index 10, Prothrombin index 78%. Modified Kline test for Syphilis, negative. Urine analysis, normal both chemically and microscopically. There were no excess porphyrins, diastase 6 Wöhlgemuth units, 17 ketosteroids, 8 mg. in 24 hour specimen. A Rous' test was positive. Examination of the faeces (twenty-four hour specimen): 82% water; of the solids 12% was fat, 35% of which was unsplit.

/X-ray ...

X-ray chest: (April 7th, 1951) Normal heart outline. Basal metabolic rate: + 6%. Electrocardiograms on March 28th, 1951 showed a variable supraventricular (probably nodal) tachycardia, together with numerous ventricular extrasystoles. The rate was 170 per minute. Within half an hour of administering 0.5 mg. of digoxin intravenously the rhythm became regular, the rate 80 per minute. During the next hour, the rate slowed to 100 per minute. Regular sinus rhythm was present. Between March 30th, 1951 and April 5th, 1951, while the patient was on digitalis therapy, a sinus rhythm persisted with slow rate. T. waves in Leads II and V_6 became flattened, and the R-St segment showed digitalis effect.

A skin biopsy was normal. A liver aspiration biopsy (carried out on April 12th, 1951 after a short course of vitamin K therapy) showed the histological features of haemochromatosis with heavy iron deposition and a moderate portal fibrosis.

Third Admission: The patient remained in good health on quinidine sulphate, 6 gr. four times daily, until May 21st, 1951, when she developed bouts of extreme paroxysmal breathlessness accompanied by 'palpitations' and was

/re-admitted ...

re-admitted to the hospital in congestive cardiac failure.

On Physical Examination: The pulse rate was 135 per minute, the rhythm was regular, and the blood pressure was 120/70 mm.Hg. The heart was not clinically enlarged. On auscultation there was a gallop rhythm.

An electrocardiogram showed a sinus tachycardia with a rate of 140 per minute. There as R-ST depression in Leads 11, V_5 and V_6 (1½ mm. in the latter). T. waves were inverted in 11, 111 aV_F and V_6 (patient not on digitalis).

Progress: She was treated with bed rest, digoxin by mouth, a salt-free diet, and mercurial diuretics. Response was satisfactory, and she was ready for discharge on June 4th, 1951.

The patient remained in good health for almost a year on maintenance digitalis and quinidine therapy. However, in August, 1952 she developed diarrhoea with marked breathlessness and pain over the right hypochondrium.

/On Physical...

On Physical Examination: She was in gross congestive cardiac failure. The pulse rate was 120 per minute, the rhythm was regular and the blood pressure was 110/70 mm. Hg. The heart was clinically enlarged, and there was a widespread protodiastolic gallop over the precordium. There were signs of a pleural effusion at the right lung base and the liver was enlarged four fingers below the costal margin and was very tender. There was gross peripheral oedema.

She was treated with digitalis, quinidine, pronestyl and bed rest but there was a steady deterioration. The pleural effusion was tapped and a venesection of 400 ccs. of blood was performed but neither seemed to influence her steady downhill course. She died in congestive cardiac failure on August 13th, 1952.

Summary of Post Mortem Findings: The body was well nourished and there was a generalized bronze pigmentation of the skin most marked over the hands and feet. There was slight pitting oedema of the lower extremities. The heart (weight 460 grams) was brown in colour and was dilated and flabby. The valves appeared normal. There was well marked congestion and oedema of the lungs; the liver weighed 2175 grams, the surface being brown and slightly granular while the pancreas, which showed well marked pigmentation, was firm and fibrotic. There

/was ...

was no obvious abnormality of the kidneys. A positive Prussian blue reaction was present in the liver, pancreas, heart, submaxillary and mesenteric lymph glands, thyroid, spleen and adrenal cortex.

Microscopically : The liver showed a moderate to marked amount of haemosiderin, the deposition being most marked in the liver and Kupffer cells. The portal tracts had small quantities of pigment, most of which lay in the phagocytes. The haemosiderin in the liver lobules was most marked in the central zones where congestion was also present. There was disappearance of a large number of liver cells. The central veins were dilated and there were small quantities of haemosiderin in the walls, mainly in the endothelial cells. In addition, there was slight thickening of the portal tracts and increased non-granular celled infiltration. The pancreas showed well marked deposition of haemosiderin in the gland cells. No islets were seen in the section which was probably taken from the head of the pancreas. The spleen had haemosiderin present in the large phagocytic cells of the pulp and the pigment was also seen lying free in the sinuses. Haemosiderin was also present in the trabeculae and connective tissues of

/the ...

the pulp. The gut showed no evidence of haemosiderin. There were slight deposits of iron pigment in the phagocytic cells of the abdominal lymph glands, whereas very little was present in the lymph follicles. Haemosiderin was also found in the connective tissue and in some of the small vessel walls. No haemosiderin was present in the ovaries and the kidney showed deposits in the convoluted tubules only. Sections of the suprarenal showed a slight amount of iron pigment in the cells of the Stratum Granulosum. There were well marked deposits of haemosiderin in the muscle fibres of the heart; the amounts, however, were variable as some cells showed large quantities while others had practically none. Some of the muscle fibres were atrophic; lipfuschin was not increased. Small quantities of iron pigment were found in the colloid and in some of the gland cells. There was no evidence of iron deposition in the brain.

CASE 3:- was a clerk aged 37 years who presented in July, 1950 with a history of tiredness, anorexia and loss of weight in the two months prior to his admission to hospital. In addition he was suffering from severe thirst and was passing large quantities of urine.

/Previous ...

Previous health had been good and he had spent 5 years in the Army. However, libido had always been poor and more recently he had become impotent. Family and systemic histories were not contributory.

On Physical Examination: He appeared underweight and ill. The hair on his head was fine and silky while axillary hair was absent and pubic hair was scanty. There was also an almost complete absence of facial hair and the skin of the face, which was thin and delicate, was covered by many fine wrinkles. There was a generalized slaty-grey pigmentation of the whole body, most marked on the exposed parts. The tongue was dry and furred and acetone could be smelt in the breath. The pulse rate was 100, the rhythm was regular and the blood pressure was 140/94 mm.Hg. There was no obvious abnormality in the cardiovascular and respiratory systems. The liver edge was felt, four fingers below the costal margin being smooth, firm and non-tender. The penis was normal in size but both testes were atrophic.

Laboratory Data: A complete blood count: Haemoglobin 14.5 gm.%, erythrocytes (per cubic millimetre) 4,640,000, leucocytes (per cubic millimetre) 11,600, neutrophils 54%, monocytes 4%, lymphocytes 39%, eosinophils 2%,

/basophils ...

basophils 1%, Blood proteins, albumin 3.9 gm%, globulin 2.8 gm%, Serum clorides 600 mgm.%, Serum diastase 121 units. Liver function tests:- Thymol turbidity, 1 unit; thymol flocculation, negative, bilirubin: direct, less than 0.5 mgm.%, total: less than 0.5 mgm.%. Icteric Index,7. Prothrombin index 100 %. Urine analysis: ++++ Sugar and acetone; no excess urobilin; diastase 10 Wöhlgemuth units; Rous' test, positive and 17 ketosteroids 16 mgm. in 24 hour specimen. Kepler-Robinson-Power test, negative. Sugar tolerance curve after 60 gm. Glucose by mouth (done after ketosis had been controlled):- Fasting level: 190 mgm.%, ½ hour, 340 mgm%, 1 hour 285 mgm.%; 2 hours 275 mgm.% . Duodenal intubation: normal pancreatic ferments. Fats in stools, normal. Basal metabolic rates: -10% and -15%. X-ray chest: Heart and lungs normal. Electrocardiogram: Inversion of T waves over V_5 and V_6 (17.7.50). Progressive diminution of T wave from V_2 to V_6 (4.8.50).

Progress: The patient's diabetes was stabilised on 25 units Protamine Zinc insulin and 20 units ordinary insulin daily. This control was accompanied by a marked improvement in general health. Subsequent progress has

/been...

been uneventful. He has been in hospital on several occasions in the past three years and further radioiron investigations have been carried out. There has been no change in his general health and the control of his diabetes has been effective.

CASE 4: was a European female who was first admitted to the Johannesburg General Hospital in May, 1948 at the age of 49 years. She was complaining of tiredness on effort for the previous two months and of difficulty in swallowing, 10 days prior to admission. Her past history was not relevant except for the history that she had been a heavy brandy and wine drinker until 2 years previously. She had six children and no miscarriages. Her periods had stopped two years previously; prior to this they had been normal.

On Physical Examination: She appeared anaemic. A striking feature was a generalized slaty-grey pigmentation of the skin, being most marked on the face, the extensor aspects of the forearms and on the legs. In addition, the skin was dry and scaly. There were no areas of pigmentation in the mouth but both tonsils were enlarged and acutely inflamed. Nothing abnormal

/was ...

was found in the cardiovascular system either clinically, radiologically or electrocardio raphically. The blood pressure was 120/88 mm.Hg. The liver was markedly enlarged, irregular in outline and non-tender. Th re were no other abnormalities found in the abdomen and pelvic examination proved negative.

The following blood count was found on admission:- Haemoglobin, 4.0 gm%; erythrocytes (per c.mm.) 1,010,000; leucocytes (p r c.mm) 11,000; polymorphonuclears 86.0%; large mononuclears, 1.5%; lymphocytes 9.5%. eosinophils 0.5%; mast cells 0; metamyelocytes 1.5% promyelocytes 1.0%. The red cells showed marked anisocytosis and increased polychromasia, as there were some punctuate basophilic cells. The following nucleated red cells were seen: 3 normoblasts, 2 megaloblasts of Ehrlich. A fair proportion of the red cells appeared macrocytic, and there was a very severe anaemia. The differential and white counts showed a polymorphonuclear leucocytosis, the polymorphonuclears showing a marked shift to the left. There was, therefore, a severe macrocytic anaemia, associated with a myeloid reaction.

Liver by injection, iron by mouth, penicillin injections intramuscularly and a number of blood transfusions completely transformed the picture, so that a

/week ....

week later the blood picture was as follows :- Haemoglobin 12.0 gm.%; erythrocytes per cmm. 3,500,000, leucocytes per c.mm. 3,700; neutrophils 59%, monocytes 2%, lymphocytes 38%; eosinophils 1%; basophils 0%.

A moderate anaemia was present, associated with a slight leucopenia. The red cells showed a marked inequality in size and shape. The majority, however, were macrocytic and hyper chromic. Giant forms about 15 cubic microns in diameter were frequently observed. In addition, scattered nucleated erythrocytes were seen; also cells showing polychromasia and punctate basophilia. The picture was that of macrocytic hyperchromic anaemia.

As soon as she had recovered from her acute tonsillar infection and the anaemia had been rectified further investigations were carried out to elucidate the nature of the skin pigmentation and hepatomegaly.

Additional Laboratory Data:- Liver function :- Thymol flocculation +++, cephalin cholesterol (after 48 hours) ++++; Icteric Index, 20 units; Serum bilirubin 0.5 mgm.%; Prothrombin Index 90%. Sugar tolerance (after 50 grams glucose orally): Fasting level, 95 mgm.%, ½ hour 130 mgm.%, 1 hour 160 mgm.%, 1½ hours 160 mgm.%, 2 hours 130 mgm.%, Blood cholesterol

/125 mgm.% ...

125 mgm.%, blood urea 50 mgm.%. Wasserman Test: negative. Urine analysis: no sugar, albumin or urobilin. 17 ketosteroids (24 hour specimen) 2.45 mgm. Iron in urine; 2.8 mgm. in 24 hour specimen. Gastric analysis, normal. Fats in stools: normal. Basal metabolic rate, + 14%. Skin biopsy: Abundant iron containing pigment in the corium.

Progress: The patient's general health improved after the initial transfusions and she remained so for the following two years. In the later months of 1950, however, she noted that she was bruisin easily and she began to suffer from recurrent nose bleeds. This bleeding became so severe that she was finally readmitted to hospital in December, 1950. The findings on this second admission were essentially similar to those previously recorded. In additon she was bleeding from the right nostril and ecchymoses were present on both forearms. The epistaxis was easily controlled and her subsequent course in hospital was uneventful. During this period radioiron absorption studies were performed on her.

Laboratory Data: Full blood count: Haemoglobin, 14.4 gms%; erythrocytes per mm. 5,070,000; leucocytes

/per m. m.

per c.mm., 5,600; neutrophils, 49.5%, monocytes 9.0%, lymphocytes 40.5%; eosinophils 1%. Sedimentation rate; 11 mm. in 1 hour. Liver function; Thymol turbidity, 1.5 units; thymol flocculation, negative; Takata-Ara (Ucko's modification) ++ positive. Alkaline phosphatase 12.2 units. Van der Bergh reaction, negative. Serum proteins 8.9 grams %. Albumin 4.0 grams% globulin. Serum bilirubin, direct - less than 0.5 mgm.%. Total, less than 0.5 mgm.%. Icteric index, 15 units. Sugar tolerance (after 50 grams glucose orally): Fasting level, 105 mgm.%, ½ hour 149 mgm.%; 1 hour, 105 mgm.%; 1½ hours 98 mgm.%; 2 hours 95 mgm.%. Serum amylase, 29 units. Urine analysis, nil chemically and microscopically except for a positive Rous' test for iron. Electrocardiogram within normal limits. Liver biopsy; heavy hepatocellular and portal iron deposits with marked cirrhosis.

Subsequent Progress: The patient was seen several times in the following year and further radioiron investigations were carried out on her. When last seen in January, 1952 she was in fair health. She complained at times during the period she was under observation of several attacks of 'palpitations' of sudden onset and accompanied by breathlessness. The description of the

/attacks...

attacks suggested some type of paroxysmal arrhythmia but no objective proof of this was obtained. An electrocardiogram in October, 1951 showed flat T waves in Lead 1 and small T waves in leads V_4, V_5 and V_6.

CASE 5, was a female, aged 53 years who was first seen in September, 1950. She had been well until three years previously when she had begun to lose her energy and to feel listless and tired. She also noticed a progressive darkening of the skin of her body, more marked on the face and arms. In May, 1950 she developed extreme thirst and went to see a doctor who diagnosed diabetes mellitus and started her on a regime of 20 units ordinary insulin and 20 units Protamine Zinc insulin daily. She subsequently went on holiday but did not feel well; her appetite was poor and she lost 28 lbs. in weight between June and August, 1950. In that month she lost consciousness and was treated by a specialist physician privately as a diabetic coma; (full details of this episode are not available). She was stabilised on 35 units of insulin daily and was feeling well and gaining weight when she was admitted to the Johannesburg General Hospital in September, 1950 for further investigations.

In the systematic history there was nothing of

/significance..

significance except in the gynaecological history. Her periods had begun at the age of 16 years but had always been grossly irregular. The time interval between periods varied from 3 - 6 months but on occasions was as long as a year. The actual loss per period seemed normal and was accompanied by marked dysmenorrhoea. She had no children, having been married after her menopause, which was at the age of 50 years. The family history was not contributory.

On Physical examination: There was a generalized slaty-grey pigmentation of the skin more marked on the exposed parts. There was no pigmentation of the mouth. Axillary hair was absent and pubic hair was scanty. The thyroid was slightly enlarged, being smooth and firm in consistency. There was no abnormality of the respiratory system. The pulse was regular and the blood pressure 126/84 mm.Hg. The heart was not clinically enlarged and the sounds were normal. The liver was two fingers enlarged and was firm and non-tender. There was no obvious abnormality of the central nervous system.

Laboratory Data: Full blood count: Haemoglobin, 12.6 grams%; erythrocytes (per cubic millimetre) 4,400,000; leucocytes (per cubic millimetre) 6,800;

/neutrophils ...

neutrophils 47%, monocytes 6%, lymphocytes 42%, eosinophils 5%, basophils 0%. Blood proteins: 3.1 grams albumin %, 2.7 grams globulin %. Serum sodium chloride 575 mgm.%, serum cholesterol 150 mgm.%. Fasting blood sugar, 270 mgm.%. Liver function: Thymol turbidity 2.5 units, thymol flocculation, negative, Takata-Ara (Ueko's modification) negative, cephalin cholesterol (24 hour reading) +++ positive. Prothrombin index 95%. Bilirubin: direct, less than 0.5 mgm.%, total, less than 0.5 mgm.%. Icteric index 10 units. A modified Ide test for Syphilis was negative. Urine analysis: ++ positive, Benedict's reaction for sugar. There was a trace of urobilin; diastase less than 7 Wöhlgemuth units, 17 ketosteroids 12 mgm. in 24 hour specimen, porphyrins no excess. Robinson-Kepler-Power test, negative. Faeces examination (24 hour specimen): no excess fat. An X-ray of the chest showed no increase in heart size, there was slight emphysema. Electrocardiogram: small T waves in lead 1 and in leads V_5 and V_6. Skin biopsy: typical features of idiopathic haemochromatosis with iron particularly in the sweat glands. Liver aspiration biopsy: heavy deposits of iron, both in parenchymal tissues and in the portal tracts. Moderate portal fibrosis with bile duct hyperplasia.

/Subsequent ...

Subsequent Progress: While in the ward she was stabilised on 60 units ordinary insulin and 40 units Protamine Zinc insulin daily. During this period radioiron absorption studies were carried out. She wad finally discharged in good health with the diabetes under adequate control. She was followed closely in the ensuing months and further studies were performed on her.

In June, 1951 she began to notice swelling on her legs and was readmitted to hospital. Findings on this second admission were essentially the same as previously, except for the presence of a mild degree of pitting oedema of the lower extremities. There were no signs of congestive cardiac failure.

It was found that she was showing ++++ sugar in the urine consistently and that the blood proteins were made up of 2.8 grams per cent albumin and 2.3 grams per cent globulin.

Difficulty was experienced in restabalising the diabetic state as her insulin requirements had risen. Stabalisation was eventually effected with a dose of 500 units insulin daily in divided doses. She was discharged without any definite conclusions having been

/reached...

reached either as to the cause of her ankle oedema or the reason for the sudden onset of insulin resistance.

She was readmitted to hospital two days later in deep hypoglycaemic coma of seven hours duration. She was given an initial dose of 60 grams glucose intravenously and responded well. Thereafter glucose was administered by mouth.

On resta alisation it was found that her insulin requirements had dropped again and she was discharged on a dose of 80 units N.P.H. insulin and 40 units ordinary insulin daily.

She was readmitted to hospital in April, 1952 for further investigations. Health had been fair in the preceding months except for a progressive loss in weight of 20 lbs.

No significant change in the physical findings was noted on examination but it was noted that she was again running ++++ sugar in the urine. In addition acetone was intermittently present on routine urine examinations. Extreme difficulty was experienced in restabalising the diabetes. Finally, she was put on a four hour schedule and was controlled on about 400 units of insulin daily. At the time of writing

/(March ...

(March, 1953) she was in good general health.

CASE 6. was a female, aged 65 years when first seen in May, 1950. The immediate cause for admission was an attack of biliousness followed by a short fainting spell on the day prior to admission. This episode had been preceded by several years of progressive breathlessness on exertion. In addition she had suffered from diabetes for 25 years; this had been well controlled in the last ten years by 25 units Protamine Zinc insulin daily. She had also been diagnosed as suffering from a peptic ulcer 5 years previously but it had responded well to medical measures.

There was nothing relevant in the systematic or family histories. She had three children; the menopause had occurred 5 years previously and had been normal.

Physical Examination: revealed an elderly woman who was acutely dyspnoeic and cyanosed. The pulse rate was 150 per minute, the rhythm was regular and the blood pressure was 240/120 mm.Hg. She was in early congestive cardiac failure. The neck veins were engorged and pulsatile one inch above the angle of Louis at an angle of 45°. The heart was clinically enlarged, the maximum cardiac

/impulse ...

impulse being in the 6th interspace in the anterior axillary line. The impulse was heaving. The heart sounds were difficult to hear because of coarse crepitations scattered uniformly throughout both lung fields. The liver was enlarged 4 fingers below the costal margin, the edge being firm and tender. There was no evidence of free fluid in the abdomen and no peripheral oedema.

Progress: The patient was regarded as an acute left ventricular failure secondary to essential hypertension and was treated with aminophylline gr. 7½ intravenously, morphia gr. ¼ subcutaneously and with oxygen. An electrocardiogram taken at the time sho ed a rate of 160 per minute, the rhythm was sinus and there was no evidence of any conduction defect. There was some depression of the ST segments with flattening of the T waves over V_4, V_5 and V_6. She responded well to treatment initially and was subsequently put on a regime of digitalis, mercurial diuretics and a salt-free diet. The diabetes was well controlled on 25 units Protamine Zinc daily. However, in the next four days she complained of several bouts of substernal pain of a cardiac ischaemic type. These attacks usually lasted 10 to 15 minutes. Five days after admission she developed

/very ...

very severe substernal pain and was found on examination to be shocked and sweaty, with a heart rate of 108 and a blood pressure of 174/94 mm.Hg. Her electrocardiogram was taken and showed the changes of a recent anterior myocardial infarction. She was started on anticoagulant therapy with dicoumarol and the prothrombin index was maintained at a level between 30 and 40%. Ten days after the commencement of this treatment she passed two large malaena stools. The haemoglobin level was 8.6 grams % and the prothrombin index on the day of the bleed was 20%. Dicoumarol was discontinued and 500 ccs. blood were given slowly intravenously. On the following day she still appeared pale and a further 500 ccs. blood was given.

Her subsequent course in hospital was uneventful and it was possible to discharge her six weeks after admission. The final diagnosis at that time was essential hypertension with left ventricular failur , acute anterior myocardial infarction and bleeding from a reactivated gastric ulcer. It was assumed that the bleeding had, in part at least, been precipitated by the anticoagulant therapy.

Second Hospital Admission: The patient was readmitted

/in ...

in November, 1950, six months after her previous discharge. She had been well until three weeks previously when she began to become breathless again on exertion. She also found that she was unable to lie flat because of the breathlessness. On examination it was noted that there was a generalised mild slaty-grey pigmentation of the skin most marked over the face and arms. She was cyanosed and dyspnoeic. The pulse rate was 78 per minute, the rhythm regular and the blood pressure 220/130 mm.Hg. She was in congestive cardiac failure, the neck veins being distended 3 cms. above the sternal angle with the patient at an angle of 45°. There were crepitations at both lung bases, the liver was 4 fingers enlarged and tender and there was slight sacral oedema. The heart was enlarged to the left, the maximum cardiac impulse being in the 5th interspace outside the midclavicular line. An early diastolic murmur was present down the left sternal border and a protodiastolic gallop rhythm was heard at the apex. Hair distribution was normal.

Progress: She was treated with digitalis leaf, mercurial diuretics and a salt-free diet. On this medication the cardiac failure was controlled. In addition she was given 25 units Protamine Zinc insulin

/for ...

for her diabetes.

In view of the skin pigmentation, coupled with markedly enlarged liver and diabetes the possibility of idiopathic haemochromatosis as an etiological factor was considered and a further series of laboratory investigations, including liver aspiration biopsy were therefore carried out.

Additional Laboratory Data: Full blood count: Haemoglobin 13.0 grams %; erythrocytes per cu.mm. 4,120,000; leucocytes per cu.mm. 9,900; neutrophils 74%; monocytes 10%, lymphocytes 13%; eosinophils 2%; basophils 2%. Sedimentation rate 52 mm. in 1 hour. Blood Proteins : 3.1 grams albumin 4.3 grams % globulin. Blood chlorides 560 mgm.%; blood cholesterol 165 mgm.%; blood calcium 9.9 mgm.%. Random blood sugar 390 mgm.%. Blood urea 150 mgm.%. Blood diastase 50 units %. Liver function: Thymol turbidity 2.5 units, thymol flocculation negative. Takata-Ara reaction (Ucko's modification) negative. Alkaline phosphatase 14.5 King Armstrong units. Icteric index 12. Prothrombin index 90%. Modified Ide test for Syphilis, negative. Urine analysis: ++ sugar and + albumin present. Fixed specific gravity at 1010. Excess urobilin present.

/Rous' ....

Rous' test for iron: negative. Less than 6.7 Wöhlegemuth units diastase. Faeces (24 hour specimen): no excess fats. Gastric analysis: histamine fast achlorhydria. X-ray Chest: The heart showed a hypertensive configuration but was not enlarged in the transverse diameter. X-rays of the long bones: Osteopo osis with osteoarthritis. Electrocardiogram: Rate 70, with sinus rhythm and no conduction defects. Conversion of T waves in standard lead 1 and in leads V1 - 6 with some digitalis effect. Liver aspiration biopsy: Heavy hepatocellular and portal deposits of haemosiderin with advanced portal fibrosis.

Subsequent Progress: In the following 3 weeks the cardiac failure remained under good control and radioiron absorption studies were carried out on her during this period.

Subsequently she began to develop bouts of colicky abdominal pain with vomiting and intermittent diarrhoea. During these attacks the serum amylase remained normal and a barium meal proved negative. The possibility of subacute intestinal obstruction was considered but repeated X-rays of the abdomen showed no evidence of fluid levels. The blood urea was constantly raised at levels between

/150 and ...

150 and 196 mgm.%. She was treated with gastric suction and intravenous fluids. However, the general condition gradually deteriorated. She developed bedsores over the sacrum and lapsed into a stuporose state and developed a pyrexia with signs of bronchopneumonia in both lung fields. She finally died on January 11th, 1951.

Post Mortem Findings: The body showed generalised wasting with bedsores on both buttocks. The skin was not markedly pigmented except for some varicose pigmentation of both lower extremities. There was extensive basal atelectasis of both lungs with a superimposed acute bronchitis. The heart was macroscopically normal (weight 300 grams) except for evidence of an old healed apical infarct. There was marked atheroma of the aorta. The stomach showed a healed gastric ulcer at the junction of the cardia and body. The mesenteric lymph glands were somewhat enlarged and were pigmented brown. The liver weighed 1920 grams and was brown in colour with marked fine nodular hepatic fibrosis. The pancreas showed evidence of a pancreatitis with fine nodularity but no pigmentation. The kidneys were contracted and the vessels were marked by atherosclerosis. The suprarenals were normal. The ovaries showed atrophic changes. The thyroid was atrophic and the brain appeared normal.

/Microscopically ...

Microscopically: There was a marked uniform degree of periportal fibrosis around each of the lobules of the liver. The fibrous tissue could be seen infiltrating round the liver cells. A large number of iron-containing granules were present in the periportal areas. In the areas where fibrosis was most marked there was evidence of new bile duct formation. These bile ducts also contained haemosiderin. The liver cells showed a heavy deposition of iron-containing pigment which was diffusely distributed throughout. The granules tended to be concentrated mostly towards the potential bile duct lumen. The amount of iron was approximately equal in the liver cells and portal tracts. Only occasional Kupffer cells were pigmented. The islets of the pancreas appeared reduced in number. Those present exhibited no obvious histological change. There was no evidence of haemosiderin in the granular tissue. The larger arteries showed thickening of the intima which contained small calcific deposits. The spleen showed a marked reduction in the number of Malpighian corpuscles; the surviving ones contained hyalined central arterioles. There was thickening of the red pulp with increased fibrous tissue between the splenic sinusoids which were relatively empty. Large areas of haemorrhage, however, were present. In spite of the haemorrhage, iron-containing macrophages

/were ...

were scanty. No abnormality of the oesophagus, or of the small and large bowels was noted. Mesenteric and para-aortic lymph nodes showed crowding of the sinusoids with macrophages containing iron pigment. The kidneys exhibited a well marked degeneration of the glomeruli with evidence of intercapillary glomerular sclerosis. Surviving glomeruli showed evidence of increased cellularity. There was intimal hypertrophy of arterioles with thickening of the internal elastic membrane. There was no evidence of iron-containing pigment. The adrenals were normal except for some reduction of the Zona glomerulosa. The thyroid contained several small adenomata with no evidence of papillary infolding. The lungs were markedly congested and the bronchi appeared normal. The hilar lymph glands showed dilation of the vessels; carbon pigment was present but no iron. The muscle fibres of the heart were broader than usual and were not pigmented. The nuclei were large and hyperchromatic. There was a slight increase in fibrous tissue between the collections of muscle fibres. No abnormality of the brain was noted.

D I S C U S S I O N.

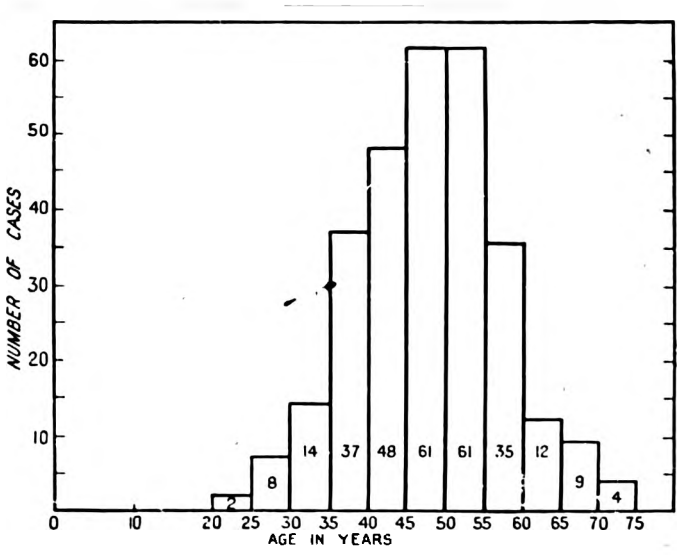
Several aspects of idiopathic haemochromatosis are reviewed in the following discussion. Special attention is directed towards the possible etiology of the condition and to the cardiac complications which may occur. However, other aspects of the disease, including the clinical presentation, pathological findings, prognosis and treatment are also discussed briefly.

ETIOLOGICAL FACTORS:

Age Incidence: The disease has a fairly limited incidence, the maximum occurrence being between 45 and 55 years, 42% of cases occurring between these ages (2). However, as can be seen from Table IV, as drawn up by Sheldon (72), isolated cases have been recorded at much earlier and much later ages. Clinically, therefore, the disease is one of middle life although it is probably present for many years before it becomes manifest.

/TABLE VI ...

TABLE VI


NUMBER OF CASES
60
50
40
30
20
10
0
10
20
25
30
35
40
45
50
55
60
65
70
75
AGE IN YEARS
2
8
14
37
48
61
61
35
12
9
4

In the cases reported here, there was a range of age from 21 to 66 years (mean 43 years). A feature of this small series was the finding of two cases in their early twenties. The significance of the early appearance of the disease in these two patients is discussed later.

Sex Incidence: Sheldon (72) found the sex incidence to be even more sharply limited than the age, there being an overwhelming preponderance in males (ratio 20 males to 1 female). This has been confirmed by later workers (4), (56) and is possibly related to the regular loss of iron in menstrual blood.

Of the 6 cases of idiopathic haemochromatosis described in the present thesis 4 were females and 2 were males. There is some doubt as to whether case 6 can be regarded as a typical case of the disease but the other three were classical. The reason for this striking reversal in the sex ratio in this series is not apparent but is to some extent invalidated by the small number. Subsequent to the present investigation two more cases of idiopathic haemochromatosis, both in males, have been seen.

/Familial ...

Familial Factors: There is no doubt that hereditary factors are of some importance in the disease. Several well authenticated reports of a familial incidence were analysed by Sheldon, and Lawrence (5) described a family in which the transmission of the disease was thought to suggest a sex-linked inheritance. In 12 of 30 cases examined by Marble and Bailey (56) diabetes was known to be present in some relative, although none had idiopathic haemochromatosis, while Althausen and co-workers (4) found the disease present in 2 siblings of the 23 cases which they studied. The most striking familial incidence was reported by Nussbaumer and co-workers (62) who found four cases in siblings. Three of these subjects were females and all exhibited signs of myocardial failure. These authors were also able to trace consanguinity of the parents, a finding pointing strongly to a transmitted genetic factor.

In the 6 cases reported in this thesis no family history could be obtained. The sister of case 3 has been diagnosed as having acute idiopathic porphyria but the possible significance of this association is not apparent.

Nutritional Status: In view of the incidence of excessive iron deposits in malnourished Bantu (35), (36), (43) and

/in ...

in rats fed on a diet low in phosphate and high in iron content, careful analyses were done by Althausen and co-workers (4) of the dietary content of the 23 cases of the disease which they investigated. There did not seem to be any reason, however, to incriminate such a factor in idiopathic haemochromatosis. Similar conclusions were reached in the present study.

The Nature of the Metabolic Fault:

At autopsy cases of idiopathic haemochromatosis may have between 25 and 50 grams of iron in the viscera, while normal subjects have only about 5 grams (72). The disease must, therefore, be associated with a steady accumulation of iron in the body which may take place over many years. To understand the possible significance of this fact it is necessary to review briefly the normal mechanism of iron absorption form the gut.

Normally the quantity of iron in the body is largely regulated by the amount absorbed from the intestine as Hahn(41) has shown that the mucosal cells of the gut have the power to "block" further iron absorption once the body's needs have been satisfied. On this basis Granick (38) has postulated that normal iron absorption depends on the presence of a protein substance, apoferritin, in the

/mucosal ...

mucosal cells of the upper intestinal tract which accepts iron from the diet and binds it into an iron protein complex called ferritin. Once such a combination has occurred in a cell then further iron absorption remains at a standstill until a plasma protein (B_1 globulin) has removed the iron from the ferritin and thus released apoferritin again. Although later studies have shown this mucosal block to be not as complete as was originally thought [27] there is little doubt that the major regulating mechanism for the quantity of iron in the body is an absorptive one, as the body seems to have only limited means for excreting the element. It has been shown experimentally that iron is not excreted by the lower bowel [40] and only very small amounts are present in the urine [53]. More recently it has been suggested that significant quantities of iron are lost in sweat [58] but later studies have not been able to confirm these findings [1], [45], [46].

In idiopathic haemochromatosis, therefore, where large deposits of iron are present in the body, it is reasonable to assume that excessive quantities must be absorbed from the gut. However, it is also possible that if this process is progressing at a slow rate over

/many ...

many years then the extra quantity being absorbed at any one time may be too small to be measurable by available experimental methods.

The pattern of iron absorption in idiopathic haemochromatosis has been investigated in the past by several workers who have done chemical iron balance studies. However, the results have been conflicting (26), (31), (54) and an abnormally large absorption s emed to be present in only two subjects (31), (54). More recently radioiron has replaced these earlier methods as a research tool in the disease but once again the results have been inconclusive as Balfour and co-workers (5) showed a very low blood uptake in one subject while Dubach and co-workers (27) found that an abnormal retention of radioiron seemed to have occurred in another. It was to investigate this problem in more detail that the present study was initially done as it was felt that there would be more chance of bringing to light a possible abnormality of the pattern of iron absorption if a group rather than individual cases were investigated. The technique was also extended to include in vivo measurements over various sites. A group of control s bjects from

/various ...

various age groups were then subjected to the same investigation. The group included both males and females (5 males and 4 females) and also three subjects with diabetes, as this is such a common feature in idiopathic haemochromatosis. Two other subjects had cirrhosis of the liver, the one having a cardiac cirrhosis while the other was of unknown etiology.

There is no doubt that the group of cases of idiopathic haemochromatosis showed a pattern of iron absorption and utilisation which was unlike that found in any of the control subjects. There was a tendency for greater absorption from the bowel to occur; in 3 subjects this was strikingly so. Only a small percentage of the absorbed iron appeared in the blood as haemoglobin, the remainder being deposited in the liver and other organs. Another interesting feature was the finding of very high absorptions of iron in the two young subjects with the disease who were investigated. In fact, with one exception, the amount absorbed seemed to be roughly inversely proportional to the age of the patient. Such a finding offers a possible explanation for the poor prognosis in younger subjects, as it suggests that the metabolic defect in such cases is a more severe one which is associated with the early appearance of clinical symptoms. In older subjects, on the other hand,

/where ....

where the absorptive pattern approximates more closely to the normal, the clinical manifestations of the disease may be delayed until middle life. It is probable that in all types of cases the error is present from birth (72). Only on such a hypothesis is it possible to explain the enormous accumulation of iron found at autopsy in idiopathic haemochromatosis.

One case in an older age group who showed a very high absorptive pattern was case 4 (second dose). There was retention of 47% of the dose of 20 mgm. iron, whereas in a previous study only 24% of the administered iron had been absorbed. The result is somewhat difficult to explain. During the months between the two studies there was a marked clinical deterioration in her condition and she began to have frequent bouts of what appeared to be paoxysmal tachycardia. Unfortunately, contact was lost with this subject and the eventual outcome is unknown. One interesting feature of this case was the fact that she had several children and gave a history of a previously normal menstrual loss. This was unlike Cases 2 and 5, who had amenorrhoea and hypomenorrhoea respectively, prior to the onset of clinical manifestations of the disease. With a regular loss of iron via the normal menstrual

/flow ...

flow it might be anticipated that the appearance of clinical symptoms could be delayed for years in spite of a high absorption of iron from the bowel.

The present study showed that idiopathic haemochromatosis is associated with an abnormally high absorption of iron. This, however, does not necessarily mean that such an absorptive defect is the primary defect in the disease.

Three possibilities must be considered :-

(1). Increased absorption and storage of iron is the primary cause of the disease and all other manifestations are secondary to this (4), (28).

(2). A primary defect in the cellular respiratory mechanism exists so that the iron present in cellular enzymes has a shorter life and is left in a form unfit for excretion (72). If such were true then the increased absorption from the bowel of iron would not be primary but secondary to an increased demand and the disease would have to be regarded as a widespread one affecting all the cells in the body.(72).

(3). *An unknown primary disturbance independently* causes an increased iron absorption and functional as well as structural changes in

/several ...

several organs.

There are drawbacks to each of these contentions. A serious objection to the view that excess deposits of iron in some organs are responsible for functional and structural alterations in these organs lies in the fact that in several other organs fairly heavy deposits of this iron pigment produce no detectable changes in function or structure. Heaviest deposits are in the liver and Sheldon (72) has found that cirrhosis of the liver is an invariable concomitant of these deposits. However, he could not correlate the degree of cirrhosis with the extent of the iron deposits and felt that the iron per se was not an important etiological factor in the development of the cirrhosis. Similar conclusions were reached by the Gillmans (36) and Higginson and co-workers (43) in malnutritional cytosiderosis. In addition several investigators have been unable to produce cirrhosis in animals by administering large amounts of iron (16), (66), (71). Furthermore, it has been shown that even in organs which are recognised to suffer most in the disease, the extent of the functional and organic impairment does not correspond to the amount of haemosiderin present (4), (72). An instance of this is the fact that the severity of diabetes, when present,

/is ...

is independent of the degree of haemosiderosis in the pancreas (4). Two possible explanations are available to explain such discrepancies. Firstly, they may be explained in part at least, on the duration of haemosiderosis in a given organ and secondly, different organs, or even the same organ in different individuals, may have unequal susceptibilities to the noxious effects of haemosiderin. In addition, the degree of iron deposition in an organ at autopsy does not necessarily reflect the constant pattern in such an organ as Finch and co-workers (28) have shown that in conditions of iron overload redistribution of iron throughout the body is continually occurring.

The second contention, viz. that the cells of the body are unable to excrete iron as propounded by Sheldon (72) seems no longer tenable as it has been shown (7),(24) that patients with idiopathic haemochromatosis can mobilise the iron stores for haemoglobin formation if they have repeated venesections carried out on them. As much as 50 litres were removed in one patient over a year (24). At the end of this time he had a normal haemoglobin level and normal serum proteins. In collaboration with Dr. B. C. Ellis (13), the author has confirmed that repeated phlebotomies are associated with a maintenance

/of the ...

of the haemoglobin level in idiopathic haemochromatosis. In addition, we have shown that the percentage of the iron circulating in the plasma which is subsequently utilised for haemoglobin formation may be increased threefold after repeated phlebotomies (13).

The last possibility is that both the increased iron absorption and the functional and structural defects in idiopathic haemochromatosis are secondary to some unknown primary factor. At the moment there is no evidence to prove or disprove such a contention. It could only be disproved if it were shown that repeated venesection, in addition to reversing the haemosiderosis is capable of inducing arrest of the organic lesions and producing at least a partial correction of the functional manifestations of the disease over a period of many years in a sufficiently large number of patients with idiopathic haemochromatosis.

PATHOLOGICAL FINDINGS

Nothing new has been added to the description of the pathological findings as detailed by Sheldon in 1935 (72). He divided them into two main groups, namely the pigment deposits and fibrotic changes.

/(a) ...

(a). Pigment Deposits.

Haemosiderin is widely distributed throughout the body affecting mostly the glands of both internal and external secretion. The greatest amounts are found in the liver and pa creas but every secreting gland may be affected. The endocrine glands are extensively involved. The thyroid and parathyroids may have heavy deposits while the zona glomerulosa of the adrenal glands and the anterior lobe of the pituitary are also usually affected. The islets of Lan, erhans of the pancreas are affected in 80% of cases. The kidney usually shows only slight to moderate deposits in the convoluted tubules and the germinal epithelium of the testes escapes all together. Deposits are absent in smooth muscle but may be heavy in striated muscle, the heart being affected in at least 90% of cases. In addition the reticulo-endothelial system is affected, with pigment in the Kupffer cells of the liver, in the spleen and in lymph glands. The bone marrow, in contrast, only has slight deposits of haemosiderin.

In addition to hae-osiderin an iron-free pigment, haemofuscin, which contains sulphur and is probably related to melanin is found in smooth muscle. So far, little is known of its significance or origin and no

/special ...

special study was made of it in this thesis. Sheldon[72] considered it identical, or closely related to the 'brown pigment' of old age and atrophy.

(b). Fibrotic Changes.

Sheldon [72] considered the presence of fibrosis of certain organs to be as invariable as pigmentation. He found that hepatic cirrhosis, usually of a hypertrophic type, was a constant feature and pancreatic fibrosis also was always present. However, Althausen and co-workers[4] recently found that cirrhosis was not present on liver aspiration biopsy sections in 3 of 14 cases which they investigated. The incidence of primary carcinoma of the liver in idiopathic haemochromatosis is significant, having been present in 7.5% of 436 reported cases while it was only found in 4.5% of 1989 cases of uncomplicated heatic cirrhosis [6]. The spleen nearly always shows some fibrosis and it may also be found in the salivary glands, heart and thyroid. There seems to be no clear correlation between the degree of pigmentation and the presence of fibrosis in an organ. [72]

CLINICAL PRESENTATION

The disease may first become manifest in various ways. The commonest presenting symptoms are :-

(a). Skin pigmentation.

(b). Diabetes Mellitus.

(c). Abdominal symptoms due to hepatic cirrhosis.

(d). Endocrine changes.

(e). Myocardial failure.

(a). Skin Pigmentation.

Pigmentation is present in more than 80% of cases (72) and has an even distribution with a tendency to greater severity over the exposed parts. It is of two types: - in about 50% of cases it has a slaty bluish-grey colour due to haemosiderin deposits and in the remainder it is deep bronze in colour being associated with an excess of melanin. However, it is possible for a combination of two types of pigmentation to be present in the same patient. The cause of the excessive melanin deposits is not clear. It is possible that it is due to some degree of adrenal failure secondary to iron deposits in the zona glomerulosa as Hellier (42) found that adrenal deposits of iron were present in all the 35 cases of idiopathic haemochromatosis with melanin

/pigmentation ...

pigmentation, whom he investigated. However, Rogers (68) in a more recent publication could show no evidence of adrenal hypofunction in a similar type of case.

In the present study 3 cases showed haemosiderin on skin biopsy, one showed melanin and another had no abnormality. The patient with excessive melanin (case1, Study 1,) had a positive Robinson-Kepler-Power response on one occasion and 8 mgm. 17 ketosteroids in a 24 hour specimen of urine.

Sheldon (72) found pigmentation of the mucous membranes of the mouth in 16.7% of 197 cases. Marble (56), however, was unable to find it in any of the 30 cases which he investigated nor was it noted in any of the subjects described in the present study.

(b). Diabetes Mellitus

Sheldon (72) found diabetes mellitus to be present in 78% of cases. Before the advent of insulin, death usually occurred within 12 months of its appearance. However, control is now reasonably easy and does not usually present any particular problems. Althausen and co-workers (4) described 18 cases with diabetes. In only 9 were there characteristic symptoms. In the remainder its presence was only manifested by a high

/fasting ...

fasting blood sugar level or by a diabetic dextrose tolerance curve.

In only one case was there any difficulty with stabilisation. Marble (56) found that the severity of the diabetic state varied considerably from case to case in the 30 cases he studied. The average requirement was somewhat greater than normal, being 60 units daily.

Only 3 of the cases described in this thesis had diabetes. Control was easy in two. In a third one (case 4) true insulin resistance was present in that the patient required between 400-600 units of insulin daily over many months. This resistance developed while she was being studied but no cause for its presence could be found. A similar type of subject requiring 1600 units insulin daily has been described by Root (69). The occurrence of such cases in idiopathic haemochromatosis, however, is extremely rare.

(c) Hepatic Cirrhosis

Hepatomegaly is the most constant presenting feature in idiopathic haemochromatosis. Sheldon (72) reported its presence in 92% of 202 cases, Marble (56) in 100% of 30 cases, while Althausen and co-workers (4) found a

/palpable ...

palpable or a suggestive resistance to be present in all except one of 15 patients. In the cases studied in this thesis it was invariably present.

The hepatomegaly is usually due to the combination of heavy iron deposits together with a hypertrophic cirrhosis. Although cirrhosis is very common it may occasionally be absent (4). Ascites and splenomegaly are common (4), while haematemesis from ruptured oesophageal varices is less frequent but may also occur (56). The commonest subjective symptom associated with the hepatic enlargement, is upper abdominal pain (47).

Cirrhosis was found to be present in all the cases investigated in this thesis. In one (case 3) it was associated with subcutaneous ecchymoses and spider naevi while it did not seem to be giving rise to any obvious clinical manifestations in the others. In a case investigated recently, but not reported here, heavy iron deposits in the liver were found to be present but were not associated with any evidence of fibrosis.

(d). Endocrine Changes

Endocrine symptoms were found to occur in a small percentage of the cases analysed by Sheldon (72). It

/is ...

is probable that they occur more frequently than was previously thought as they were not specifically sought in many of the earlier reported cases. Marble (56) found them to be common in those cases studied from this point of view, Althausen and Kerr (2), (3) reported them in 20 out of 115 cases and they were present in 4 of the 6 cases which were studied in the present investigation.

The clinical picture is essentially that of a mild "Simmonds" type with fine skin, loss of secondary sexual hair and testicular atrophy with impotence. In addition the hair of the head is usually soft and silky and the need for both hair-cutting and shaving is often much less than normal while in females oligo and hypomenorrhoea may be present. The basal metabolic rate is lowered in some of these cases (63) and one case has been reported (73) in which signs of hypoparathyroidism were present with a low blood calcium and tetany.

No very detailed endocrine studies have been carried out as yet in idiopathic haemochromatosis. It has been suggested that the endocrine changes may be secondary to damage caused by deposits of iron in the anterior pituitary (3), (4). It is also possible that localised deposits in the zona glomerulosa of the adrenal cortex may be a

/contributing ...

contributing factor in some cases. The role of liver damage in the development of endocrine disorders is not clear. It has been shown experimentally that sexual regression may occur secondary to the distrubed oestrogen: androgen balance which occurs with liver damage (59). Similar findings have been found in malnourished Bantu with liver disease (36). However, Althausen and coworkers (4) feel that this explanation is less likely to hold in idiopathic haemochromatosis where liver function is relatively good as compared with other forms of portal cirrhosis.

Four cases in the present study showed evidence of endocrine dysfunction. There was sparsity of the secondary sexual hair in all these subjects. Impotence, with testicular atrophy was present in both the males. In the younger female there was a history of complete amenorrhoea secondary to the birth of her only child several years before and there had been gross oligo and hypomenorrhoea previously in the other who was post menopausal, when studied. The basal metabolic rate was low in both the males. The quantity of 17 ketosteroids in the urine was lowered in only one patient (case 4) and she showed no obvious signs of endocrine abnormality while the Robinson-Kepler-Power test was negative in all except one patient (case 2).

/(c) ...

(e). Myocardial Failure.

Although the other signs of idiopathic haemochromatosis have been extensively described, little mention has been made of the cardiac complications of the disease in the English and American literature. Sheldon (2) mentioned that "several cases have died from cardiac failure but on the whole the extensive deposits laid down in this organ produce little clinical evidence of their presence". French writers have, however, recognised the occurrence of myocardial failure in idiopathic haemochromatosis for many years and Oulin (15) in a statistical survey of 70 cases found that cardiac failure was observed in 17.5% and that the electrocardiogram was normal in only 22.7% of cases. Shulze-Buschoff and co-workers (74) have also recorded recently that although clinical signs in the heart are not common in the disease, electrocardiographic changes are frequently seen, being present in 14 out of 15 cases studied.

Although little attention has been paid to the cardiac complications of haemochromatosis, a fair number of case reports have accumulated in the past few years. The majority of these have been set out briefly in Table form to show the salient points (Table VII).

/The ...

TABLE VII.

Name		Sex	Age	Skin Pigmentation	Glycosuria	Hepatic Enlargement	Sexual Hypoplasia	B M R	Cardiac Abnormalities	Cause of Death	Pathological Findings
Marsh	25	M	28						Heart was enlarged to percussion. Multiple extrasystoles	Diabetic coma	Heart weighed 400 gm. Rt. ventricle proportionately larger than left. Yellowish brown colour. Atrophy of muscle wall. Microscopy showed marked fibrosis and haemosiderin deposits
Althausen and Kerr	1	M	53		−			+34% + 5%	Blood pressure, 96/70 mm. Hg. E.C.G.: PR of .19 second. Flattened T_1 T_3 diphasic. Developed C.C.F.		
Wood & FitzHugh	35	M	48		+	+	+		Marked functional depression of myocardium on E.C.G.	Ruptured duodenal ulcer	Haemosiderin in heart. Nil else
Berancon, de Gennes, Delarue, Oumansky	4	M	20		+	+	−	−	Breathlessness on exertion and asthma. Pulse 140, regular. Gallop rhythm.	C.C.F.	Heart large and flabby. Dilated. Muscle brown in colour.
Althausen and Kerr	2	M	59	+	+	+	+		Heart moderately enlarged. E.C.G.: low voltage. Left axis deviation. Flattened T_1 T_3	C.C.F.	Haemosiderin present in heart. Diffuse sclerosis of vessels
		M	43	+	+	+	+	−	Auricular fibrillation. Blood pressure, 132/84 mm. Hg.	—	—
		M	21	+	+	+	+	−17%	Cardiac enlargement and auricular fibrillation	Congestive cardiac failure	—
New England Medical Journal Discussion	10	M	36	+		+	+		Presented as C.C.F.; E.C.G., slurred QRS and left axis deviation	Died suddenly during an attack of paroxysmal auricular tachycardia	Heart weighed 450 gm. Marked deposition of iron
de Gennes, Delarue et de Vericourt	17	M	35	+		+	+	−28%	Patient had increasing dyspnoea on exertion. No E.C.G. Heart + +. Blood pressure, 100/70 mm. Hg.	C.C.F.	—

TABLE VII (Continued)

Name		Sex	Age	Skin Pigmentation	Glycosuria	Hepatic Enlargement	Sexual Hypoplasia	B M R	Cardiac Abnormalities	Cause of Death	Pathological Findings
Maling & Riley	24	M	50	+		+			E.C.G., low voltage. Flattened T wave in all three leads. Blood pressure, 90/70 mm. Hg. Large heart on X-ray	C.C.F. with auricular fibrillation	Heart greatly enlarged. Wall brown and friable. Coronary arteries and valves healthy. Haemosiderin on microscopy. Diffuse fibrosis of myocardium
Germain et Morvan	19	M	46	+		+			Dyspnoea on exertion. Extrasystoles. C.C.F.	—	—
Blumer & Nesbitt	5	M	54	+		+			Marked C.C.F. No E.C.G.	C.C.F	Weight of heart 410 gm. Pigmentary infiltration and myocardial fibrosis. Coronary arteries healthy
Donzelet et E. de Vericourt	15	M	26	+	+	+	+		Increasing dyspnoea. Presystolic gallop. Blood pressure, 100/60 mm. Hg. E.C.G., low voltage, inverted T waves in leads I and II	—	—
Flaum & Stueck	16	M	39	+	+	+	+		C.C.F. with gallop rhythm. E.C.G. showed normal PR interval, QRS normal, T wave diphasic in lead I, inverted in lead III	C.C.F.	Moderate dilatation of heart especially of rt. ventricle. Weight 400 gm.
Kepler, Nichols & Mills	21	M	47		+	+	+		E.C.G., iso-electric T wave in lead I. Diphasic T waves in leads II and III. Sinus tachycardia	Died at home. ?cause	—
Cain	9	M	?	—	+	+	+	−12%	Cardiac enlargement + many extrasystoles. No E.C.G.	Generalized weakness. Carcinoma of prostate	Slight cardiac hypertrophy. Haemosiderin in muscle. Arteriosclerosis
de Gennes et Germain	18	M	40	+	+	+			Some dyspnoea. No oedema. Heart + . Blood pressure, 110/80 mm. Hg.	C.C.F.	Heart large and flabby. Wt. 450 gm. Degenerative myocarditis with + + haemosiderin deposits

TABLE VII (Continued)

Name		Sex	Age	Skin Pigmentation	Glycosuria	Hepatic Enlargement	Sexual Hypoplasia	B M R	Cardiac Abnormalities	Cause of Death	Pathological Findings
Clerc, Bascourret, Andre	11	M	36	+	+	+			Dyspnoea on exertion. Some cyanosis. Heart + +. Presystolic gallop. Some right axis deviation. Flattening of T wave in I and II		
Bouchut *et al.*	6	M	40	+		+			Attacks indistinguishable from coronary thrombosis followed by C.C.F. Heart + +. Gallop rhythm. Blood pressure, 110/70 mm. Hg: Responded for a time to digitalis	C.C.F.	Heart weighed 680 gm. Widespread deposits of haemosiderin, both parenchymatous and interstitial
		M	33	+	+	+			Subject to anginal attacks. Persistent tachycardia. Some signs of C.C.F.	Coma	Heart weighted 410 gm. Adherent pericardium. Diffuse pigmentation of both muscle fibres and interstitial tissues
Lyon	23	M	27	+	+		—		C.C.F., no details	C.C.F.	Gross dilatation of heart. No organic valvular lesions. Heavy iron deposits
		M	54	+		+			Blood pressure, 105/75 mm. Hg. Attacks of paroxysmal ventricular tachycardia. E.C.G., left sided preponderance and rt. ventricular extrasystoles	Sudden collapse	Great enlargement of heart due to dilatation. Vessels and valves healthy
		F	34	+		+	+		Clinically C.C.F.; E.C.G., prolonged PR interval. Low voltage, ventricular extrasystoles. Blood pressure, 110/70 mm. Hg.	C.C.F.	Enormous dilatation of heart; + haemosiderin. Vessels and valves healthy
Coats	13	M	38	+	+	+	+	—	Increasing dyspnoea on exertion. Swelling of ankles. Blood pressure, 98/70 mm. Hg	Generalized weakness	Left ventricle dilated. Haemosiderin present in heart
Labbe, Boulin *et al.*	22	F	45	+					Cardiac insufficiency shown by gallop rhythm. E.C.G., low voltage with widening of QRS complexes		

TABLE VII (Continued)

Name		Sex	Age	Skin Pigmentation	Glycosuria	Hepatic Enlargement	Sexual Hypoplasia	B.M.R.	Cardiac Abnormalities	Cause of Death	Pathological Findings
		M	35		+				Cyanosis — marked oedema. Blood pressure imperceptible	C.C.F.	Heart showed inflammatory nodules with oedema but no trace of pigmentary infiltration
Balfour *et al.*	3	M	49	+	+	+	-	-43%	Myocardial damage	—	—
Stroder	33	M	17			+	+		Advanced C.C.F. Heart +. E.C.G., extrasystoles and varying degrees of heart block	C.C.F.	Heart showed myocardial fibrosis and widespread pigment deposits
		M	30	+		+	+		Blood pressure, 130/75 mm. Hg. Dyspnoea on exertion. Extrasystoles. Early C.C.F. E.C.G., myocardial damage		
Gray	20	M	68	+		+		-18%	E.C.G. showed evidence of myocardial damage 6 years before death. Developed C.C.F. two years later	Liver damage. Carcinoma of liver	All chambers of heart dilated. Muscle flabby and brown. Vessels healthy. Haemosiderin microscopically
Petit	29	M	35	+		+			Developed C.C.F. Heart enlarged to left. Blood pressure, 110/80 mm. Hg. E.C.G., complete A-V block with low voltage ventricular complexes, abnormal T waves and right axis deviation	?	Heart valves and coronary arteries normal. Microscopy: localized area of atrophy in the myocardium. Numerous broad spaces between muscle fibres containing fibroblasts
Tucker *et al.*	34	M	31	-	+	-	+		Developed C.C.F.; E.C.G., premature ventricular contractions, low voltage QRS. Deep S_1 S_2 diphasic T_1 - T_2	C.C.F.	Heart dilated. Coppery brown in colour. Microscopy: cells swollen, pigment present. Some replacement of cells by connective tissue but no dense fibrosis
Clinico-Pathologic Discussion. Amer. J. Med.	12	M	54	+	+	+	+		Developed C.C.F.; E.C.G., abnormal ventricular complex. Low voltage. Sinus bradycardia	C.C.F.	Increased connective tissue + fat in interstitial tissues. Haemosiderin deposits

The most striking feature of the Table is the regularity with which myocardial damage, when present, is coupled with enlargement of the liver and with genital changes, the association being present in 22 out of 33 cases. This pattern was recognized by Bezancon and co-workers (8) as the Endocrine-Hepatic-Cardiac Syndrome of haemochromatosis.

As can be seen in Table VII the exact nature of the cardiac symptoms and signs varies from case to case. The only constant feature has been the poor prognosis, once cardiac symptoms have appeared. In those cases which were followed to death there was an average survival period of less than one year after the onset of cardiac symptoms. Response to digitalis was almost uniformly bad. Disorders of rhythm were present in most cases. Extrasystoles were common but any form of arrhythmia may be seen .

In most cases with myocardial damage congestive cardiac failure occurred terminally. Sudden death during an attack of paroxysmal tachycardia was recorded in one case.

Electrocardiographic findings follow no definite pattern. In most cases they show evidence of myocardial damage. Bolin (15) in a review records low voltage curves, left axis deviation, flattening and inversion of T waves and various arrhythmias. A fairly constant feature has been the occurrence of low voltage tracings. The arrhythmias which may occur include auriculo-ventricular block, paroxysmal auricular, nodal and ventricular tachycardia, auricular flutter and auricular fibrillation (44), (65), (78).

Radiographically the heart is often diffusely enlarged being similar in appearance to that in Beri-beri or acute rheumatic carditis (78). Pathologically, all chambers are diffusely enlarged due to hypertrophy and dilation and the myocardium is flabby and shows brown pigmentation.

The average age at death of the cases with myocardial damage, listed in Table VII was 38 years as compared with an average age of onset of between 45 to 50 years

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in those patients without clinical evidence of heart involvement (72).

On this evidence it appears that a diagnosis of idiopathic haemochromatosis should be considered in any patient who develops an unexplained heart failure below the age of 40 years, especially if the patient exhibits signs of endocrine hypofunction and has a firm, enlarged liver. Skin pigmentation is not always present in such cases (10), (62) and glycosuria is often absent so that diagnosis may be difficult.

The present study included 2 cases of idiopathic haemochromatosis who presented primarily with heart failure. The one was a male (case 1, Study 1) and the other a female (Case 1, Study 11). Clinically the two cases were very similar. Both were in their early twenties, had evidence of sexual hypoplasia, and showed advanced myocardial damage with bouts of paroxysmal arrhythmia. In case 1 (Study 1) there was, however, no evidence of skin pigmentation. The female, (Case 1, Study 11) was also interesting in that only two other women have previously been reported with such a clinical presentation (52), (64). Both were young (34 years and 18 years, respectively) and in both amenorrhoea was

/the ...

the initial symptom. Skin pigmentation and hepatic enlargement were present, but sugar tolerance was normal.

Both the electrocardiograms in the two cases investigated in the present study showed evidence of myocardial damage. In case 1 (Study 1) there was a constant reduction in amplitude in standard leads 1-111 while the chest leads CR_{1-6} were characterised by large inverted T waves in positions 1-4 and T waves, which were practically isoelectric in positions 5 and 6. (see Figure X1). In addition this patient was subject to bouts of paroxysmal ventricular tachycardia (see Figure X11). In the other subject, (Case 1, Study 11) there was R-ST depression in leads 11, V_5 and V_6 (1½ mm. in the latter). T waves were inverted in leads 11, 111 AXF and V_6 (see Figure X111). On one occasion an electrocardiogram was recorded while this patient was exhibiting a bigeminal rhythm (see Figure X1V). However, it was found that there was also a tendency to flattening of the chest leads over the left side in the other cases investigated who exhibited no signs of myocardial failure (see Figure XV).

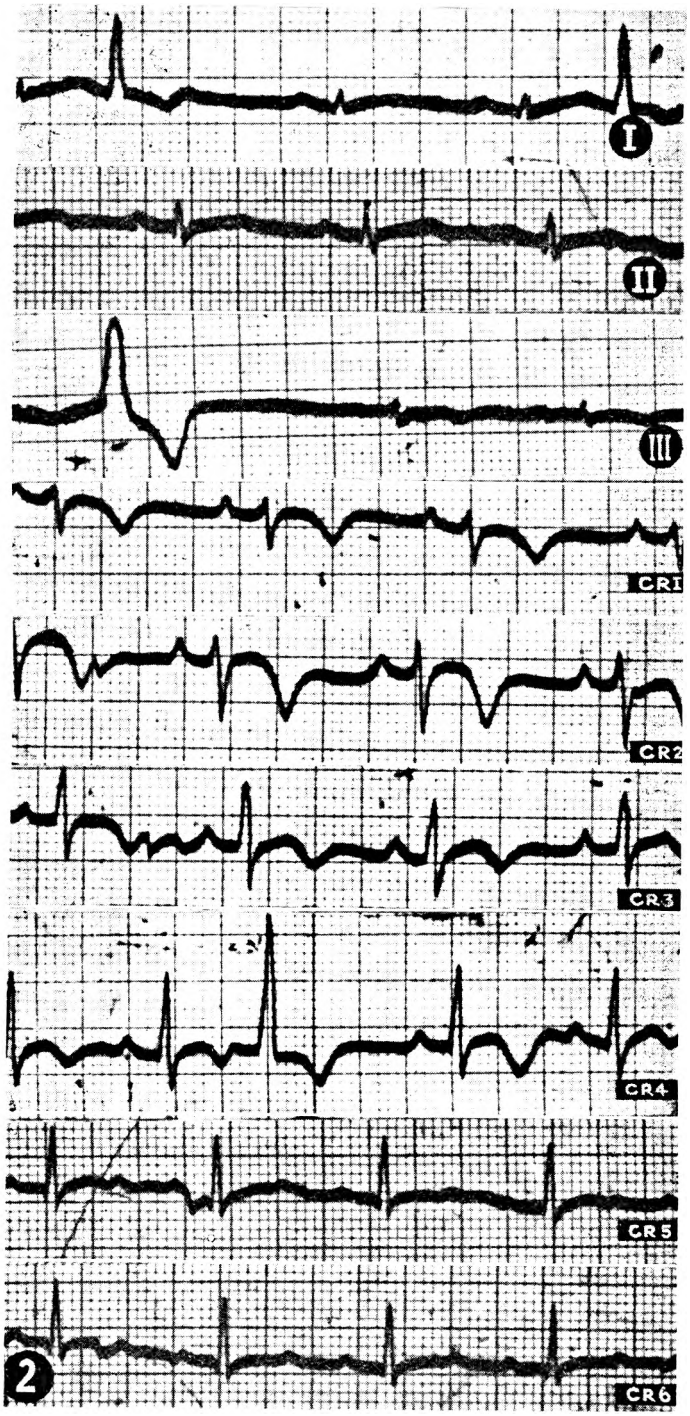

FIGURE X1 - Electrocardiogram in case 1 (Study11) showing low voltage in leads 1 to 111 and large inverted T waves in leads CR 1-4.

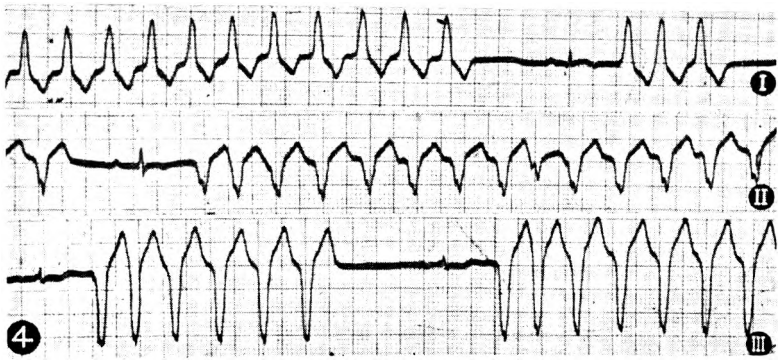

FIGURE XII - Electrocardiogram Case 1 (Study 1) taken during an attack of paroxysmal ventricular tachycardia.

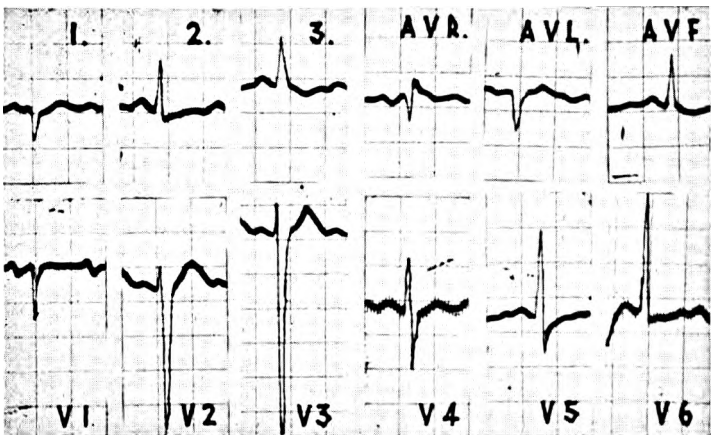

FIGURE XIII - Electrocardiogram on Case 1 (Study 11) showing a sinus rhythm with flat T waves in Leads 11, AVF and V_5.

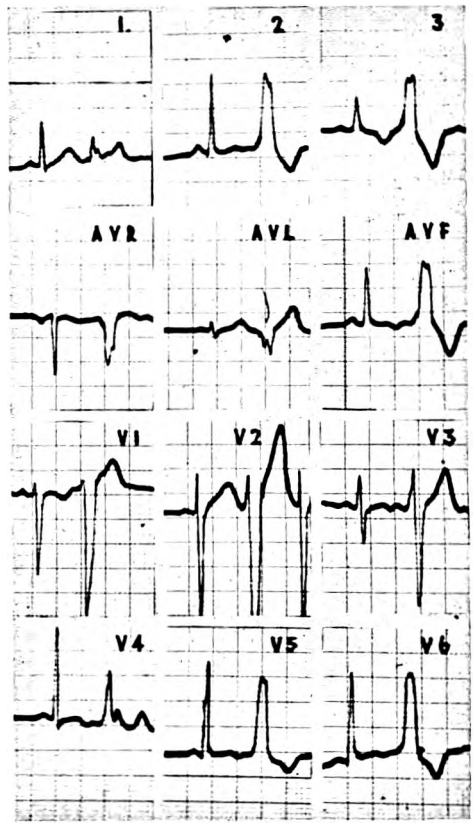

FIGURE XIV - Electrocardiogram on Case 1 (Study 1) showing a bigeminal rhythm.

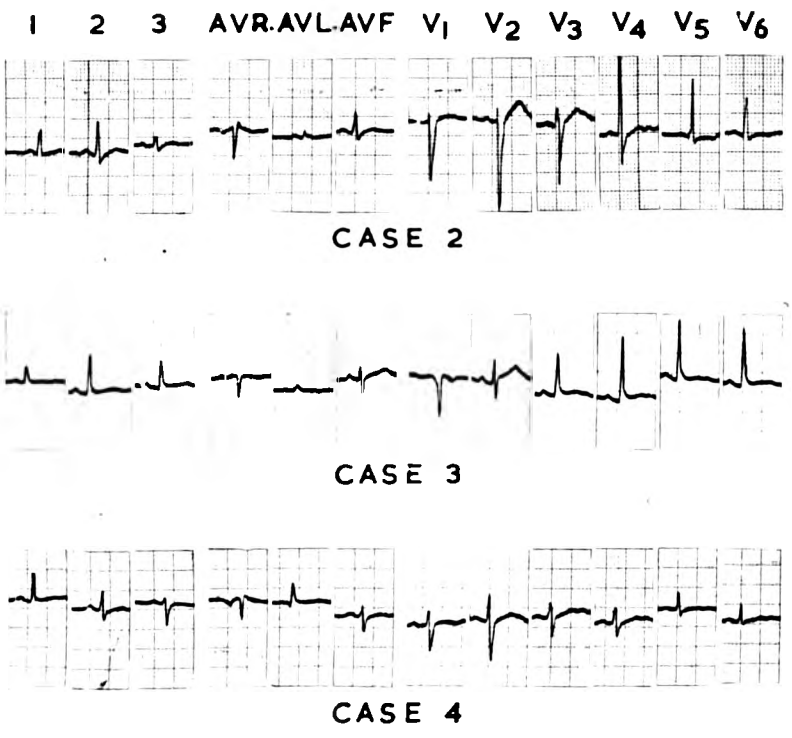

FIGURE XV - Three electrocardiograms on cases of idiopathic haemochromatosis with no signs of cardiac damage.

Although the occurrence of myocardial failure in idiopathic haemochromatosis is now well recognised, its cause is still not known. The post mortem findings in all but one case (33) showed varying degrees of deposition of iron containing pigment. Cardiac hypertrophy was recorded in most cases but was usually not excessive. Fibrosis of the myocardium has been reported by several authors (9), (44), (65), (73), and attempts have been made to correlate the congestive failure with the extent of the microscopic anatomical findings (9),(44),(51), (65),(75). An almost constant feature has been the presence of iron deposits in the heart muscle. However, there does not seem to be any direct correlation between the degree of iron deposition and the severity of the cardiac symptoms. In addition it must be remembered that 90% of cases with idiopathic haemochromatosis have iron deposits in the heart muscle while only a small proportion develop myocardial failure (72). The seeming anomaly of these findings has led several French authors to invoke endocrine factors to explain the cardiac failure (20),(32).

In the radioiron studies which were carried out in the present investigation evidence was obtained which may possibly explain the frequent occurrence of heart

/failure ...

failure in young patients suffering from idiopathic haemochromatosis. It was found that both the young subjects with evidence of severe myocardial damage had very high uptakes of iron from the gut. In one (case 1, Study 1) 62% of a dose of 34 mgm. was retained in the body, while 72% of a dose of 20 mgm. was absorbed in the other. In addition, in vivo counts over the heart in both subjects seemed to show that an appreciable proportion of the absorbed dose was being deposited there as the counts obtained were considerably higher than could be accounted for by radiation "scatter" from the liver.

Figure XVI illustrates this finding in case 1, (Study 11).

/FIGURE XVI...

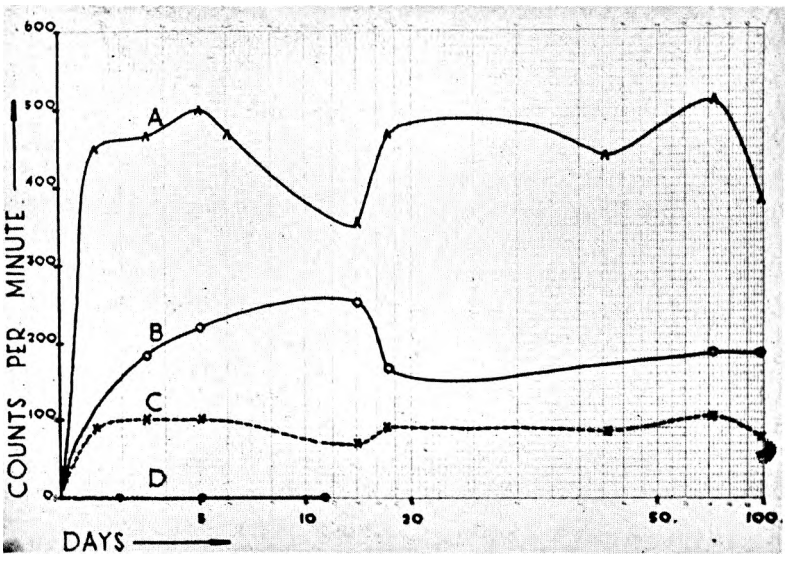

FIGURE XVI - Graph showing counts obtained over mid-heart and mid-liver in Case 1 (Study 1) and in a representative control subject. A = counts over mid-liver in patient; B = counts over mid-heart in patient; C= predicted curve to be expected over mid-heart of patient due to radiation "scatter" from liver; D = counts over mid-heart and mid-liver of control subject.

It is therefore felt that the much higher incidence of heart failure in the younger age group may possibly be related to the fact that the disease is present in a more acute form in which iron is being absorbed and deposited at a much accelerated rate. On this basis, the damage to the myocardium would not be related so much to the degree of iron deposition as to the rate at which it is being laid down. It would thus be possible to explain why patients with heavy iron deposition in the cardiac muscle have shown no clinical signs of myocardial damage, while others with less iron deposition have had extreme and irreversible heart failure.

THE DIAGNOSIS OF IDIOPATHIC HAEMOCHROMATOSIS

In a case presenting the whole clinical picture the diagnosis is obvious. Difficulty arises in the absence of one or more of the symptoms. Where the possibility of idiopathic haemochromatosis is suspected several diagnostic procedures are available :-

(a). Liver Aspiration Biopsy. This is positive in all cases. However, its use is not without dangers and for this reason less hazardous procedures should be used initially in a suspected case.

/(b) ...

(b). Skin Biopsy. Granules of haemosiderin are found especially in sweat glands in about 50% of cases. Less satisfactory is the intradermal injection of acidified potassium ferrocyanide as suggested by Fishback (29).

(c). Gastric Biopsy. This was shown by Althausen and co-workers (4) to be more reliable than skin biopsy. It is, however, too dangerous for routine use.

(d). Rous' Test (70). The demonstration of haemosiderin in the cells of the urinary sediment is possible in some cases. In the present study the test was positive in three cases.

(e). Serum Iron Estimations. Iron is transported through the plasma bound to the β_1 globulins. Normally the globulin is only about one third saturated with iron (67). However, in most cases of idiopathic haemochromatosis, the percentage saturation is much higher, although the total iron binding capacity of the serum is reduced (67). This finding was confirmed in three cases investigated in the present thesis, and in another case (E.D.) of idiopathic haemochromatosis not reported here (see Table VIII).

/TABLE VIII ...

T A B L E VIII

Case	Serum Iron	Total Iron Binding Capacity	Percentage Saturation
	Normal ± 100 micrograms %	Normal ± 300 micrograms %	Normal ± 33%
1 (Study 11)	155	180	86
2	147	197	75
4	169	169	100
E.D.	130	155	86

Recently Gitlow and Beyers[37] have introduced a further test for the diagnosis of haemochromatosis, using serum iron estimations. They measured serum iron and then gave a standard dose of iron intravenously and measured the serum iron again at 5 minutes and 2 hours afterwards. It was found that the ratio of the decrease in serum iron to the previous increase was far greater in idiopathic haemochromatosis than in normal subjects and patients with other forms of cirrhosis. No confirmation of these results is, so far, available.

THE COURSE AND PROGNOSIS OF IDIOPATHIC HAEMOCHROMATOSIS

In 1935 Sheldon (72) found that the period between the time that medical advice was first sought to death was about 18½ months. The poor prognosis was largely due to inadequate diabetic control, as most cases died in diabetic coma. The survival period has been lengthened considerably with better treatment of the diabetes and Marble (56) has recently shown that patients with diabetes live for an average of 5 years. However, the prognosis is still relatively poor as the remaining features of the disease continue to progress, with the result that there is an increasing tendency for patients to die either from hepatic cirrhosis or from cardiac failure (73). As has been pointed out in a previous section, the onset of cardiac failure is an extremely grave prognostic sign.

THE TREATMENT OF IDIOPATHIC HAEMOCHROMATOSIS

Until recently no specific therapy, apart from the control of diabetes and supportive dietary measures, was available in the disease. Two possible lines of treatment suggest themselves :-

/(1) ...

(1). To prevent, by appropriate measures, the high absorption of iron from the gut.

(2). To mobilise and remove iron deposits already present.

In the present study an attempt was made, based on experimental evidence, (48), (77), (78), to 'block' the absorption of iron from the gut by the use of phosphates and fat soluble vitamins. Although used in large doses they seemed to exert no significant effect and do not seem to warrant further trial.

The second possibility, viz., to mobilise iron deposits seems more promising. Both Davis and Arrowsmith (24) and Gitlow and Beyers (37) have demonstrated that patients with idiopathic haemochromatosis are able to mobilise iron for haemoglobin formation when they are repeatedly venesected. One case tolerated well a removal of 50 litres in a year and during this time there was both subjective and objective improvement in his condition (24). This approach has been followed by the a thor together with Dr. B.C. Ellis (13) in two cases. In one it has been found that the haemoglobin level has been maintained at a level of 14 grams % in spite of the removal of 7,000 ccs. blood in 3½ months. In the other case, however, it seems that the iron stores are not

/as ...

as readily utilisable as she has developed a hypochromic anaemia after several phlebotomies. Such therapy may therefore only be available for use in selected cases. Whether its ultimate effect on the course and prognosis of the disease will be a significant one, remains uncertain. However, it seems rational enough to deserve further trial.

/SUMMARY ...

SUMMARY AND CONCLUSIONS.

(1). Clinical data on 6 cases of idiopathic haemochromatosis are presented.

(2). The etiology of the disease is discussed. Evidence is produced to suggest that the disease is an inherited metabolic defect. Radioiron absorption investigations which were done in the present study show that idiopathic haemochromatosis is associated with an abnormally high absorption of iron from the gut. It is not yet certain whether this defect is the primary one in the disease.

(3) The clinical presentation and pathological findings are discussed with special reference to cardiac complications. It is shown that such complications are common in younger subjects. It is suggested that heart failure is caused by a more acute form of the disease and that it is related more to the rate at which iron is laid down in the cardiac muscle than to the absolute quantity deposited.

(4) The diagnosis and prognosis are discussed and attention is drawn to the possible benefit of repeated venesections in the treatment of the disease.

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C H A P T E R 111.

THE RELATIONSHIP OF MALNUTRITIONAL CYTOSIDEROSIS TO IDIOPATHIC HAEMOCHROMATOSIS.

The occurrence of widespread deposits of iron in the viscera of a considerable proportion of Bantu subjects was recognised as early as 1929 by Strachan [26] and later studies have confirmed these findings [3], [9], [11], [16]. The Gillmans examined the livers of 275 apparently healthy cases who had died from trauma and found abnormally large quantities of iron in 41%. They also carried out serial liver biopsies in a group of Bantu pellagrins and were able to demonstrate heavy accumulations of iron in the livers of a large percentage of their subjects [10], [9]. In the later stages of the condition the heavy deposits of iron, coupled with portal fibrosis, gave microscopic findings indistinguishable from those seen in idiopathic haemochromatosis. They named the condition cytosiderosis and considered that malnutrition was an important etiological factor in its development. The iron pigment haemosiderin, they renamed cytosiderin to denote its cellular origin. The term malnutritional cytosiderosis has been adopted in the following section to denote this condition of abnormal iron storage which is so common in Bantu subjects.

/Later ...

Later workers (16), have confirmed the Gillmans' findings but some controversy exists as to the exact pathogenesis of the condition and to its possible relationship to idiopathic haemochromatosis. In order to examine these conflicting views more thoroughly it is necessary to review briefly the clinical presentation and pathological findings and to compare them with those found in idiopathic haemochromatosis.

CLINICAL MATERIAL -(Group 11)

CASE 6. was a Bantu Male, aged 47 years, who was admitted to hospital with a three months history of loss of weight. In the two weeks prior to admission he had also developed a marked anorexia accompanied by increased thirst and frequency of micturation. Vague abdominal pain had also been present but no special relationship of this pain to meals could be elicited.

There was nothing of note in the systematic history. His staple diet consisted of porridge and vegetables with meat at the week-ends. Consumption of 'kaffir' beer was heavy.

On Physical Examination: He was found to be darkly

/pigmented ...

pigmented, especially on the exposed parts, with some roughness of the skin. There was no pigmentation in the mouth. The tongue was moist. The pulse was 86, the rhythm regular and the blood pressure 150/90 mm.Hg. There were no obvious abnormalities in the cardiovascular or respiratory systems. The liver was enlarged five fingers below the costal margin, the edge being sharp, firm and slightly tender. No spenomegaly was detected. There was evidence of some peripheral neuritis; there was calf tenderness with absent knee and ankle jerks.

The routine urine examination carried out on admission showed ++++ sugar, ketonuria, and a trace of albumin. Therapy was therefore commenced immediately with soluble insulin and with fluids by mouth. After several days the diabetic state seemed to be satisfactorily controlled on 100 units soluble insulin and 50 units Protamine Zinc insulin daily. In view of the hepatomegaly, skin pigmentation and diabetes the possibility of cytosiderosis was considered and investigations, with this in view, were carried out.

Laboratory Data: Full blood count: Haemoglobin 12.7 grams %. Erythrocytes per cu.mm. 4,260,000; leucocytes per cu.mm. 6,200. Blood Proteins: 2.9 grams % albumin, 5.6 grams % globulin. Serum

/sodium ...

sodium 337 mgm.%, serum chloride 530 mgm. %, serum potassium 20 mgm. %, serum calcium 9.5 mgm. %. Blood urea 28 mgm. %, blood diastase 127 units; blood cholesterol 120 mgm. %. Sugar tolerance curve (after 50 grams glucose). Fasting level, 160 mgm. ½ hour 175 mgm. , 1 hour 210 mgm.%, 1½ hours 240 mgm.%, 2 hours 230 mgm.%. Liver function:- Thymol turbidity 3 units, thymol flocculation +++ positve, Takata-Ara reaction (Ucko's modification) +++ positive, cephalin cholesterol flocculation +++ positive. Bilirubin, less than 0.5 mgm.%. Icteric index 92%. Modified Ide test for Syphilis: negative. Urine analysis: ++++ sugar, ketonuria and ++ albumin. Diastase 22.4 Wöhlegemuth units. Faecal analysis: no excess fats. X-ray Chest: no abnormality of heart or lungs. Liver aspiration biopsy: Advanced portal cirrhosis with heavy iron deposits in the portal tracts and in the Kupffer cells. Scanty deposits were also present in parenchymal cells.

Progress: In the ward the patient was put on a high carbohydrate, high protein diet. Insulin was required initially in doses of ± 150 units daily. He responded well in the first two weeks; appetite returned and the polyuria disappeared. After three weeks, however, he had an episode of hypoglycaemic coma with

/generalised ...

generalised epiliptiform convulsions; the attack responded dramatically to 40 ccs. intravenous glucose. The dosage of insulin was subsequently progressively reduced and in the following month he remained under good control. During this period radioiron absorption studies were performed on him.

After 6 weeks' hospitalisation there had been a marked improvement in his general condition. The diabetes was adequately controlled on a 1600 calory diet without insulin. The liver regressed in size until it was only enlarged 2 fingerbreadths below the costal margin and signs of peripheral neuritis disappeared. A repeat sugar tolerance curve done 2 months after the initial one gave the following results : Fasting level 138 mgm. %, ½ hour 142 mgm. %, 2 hours 140 mgm. %. At this stage he was discharged from hospital and has not been seen since.

CASE 7. was a Bantu female aged 55 years who was admitted to hospital with a history of progressive weakness in the previous two months. In addition she had been drinking excessive quantities of water and had been passing greater q antities of urine more frequently than in the past. On one occasion she had tasted her urine and had found it to be sweet.

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There was nothing of significance in the systematic histo y. She was post menopausal and had two children who were both alive and well. Her diet consisted of meat, fruit, porridge and bread daily; vegetables were only taken occasionally.

On Physical Examination: There was evidence of generalised weight loss, the skin being dry with some desquamation over exposed parts. There was also excessive pigmentation of the skin of the face, arms and lower limbs. There was a left sided cataract. The tongue was moist and the teeth carious. No pigmentation was found in the mouth. There was a slight generalised enlargement of the thyroid gland. The pulse rate was 84 per minute with a locomotor brachial in each arm. The rhythm was regular and the blood pressure 125/70 units mm. Hg. There was no clinical evidence of any abnormality in either cardio-vascular or respiratory systems. The liver was grossly enlarged, the lower border being felt 5 fingers below the costal margin. The edge was firm and non-tender. There was no peripheral neuritis.

On admission it was found that the urine contained ++++ sugar and acetone and a blood sugar taken at the

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same time gave a result of 360 mgm.%. The acetonuria was readily controlled on a six hourly schedule of ordinary insulin.

In view of the physical findings, additional tests were carried out to find out whether she was s ffering from cytosiderosis.

Laboratory Data: Full blood count: Haemoglobin 15.4 grams %; erythrocytes per cu. mm. 5,480,000. leucocytes per cu.mm. 7,300; neutrophils 49%, monocytes 5%, lymphocytes 40%, eosinophils 5%, basophils 1%. Blood proteins : 3.2 grams % albumin, 4.0 grams % globulin. Serum sodium 336 mgm.%, serum chloride 565 mgm. %; serum calcium 9.9 mgm.%, serum potassium 20.4 mgm.%, serum diastase 164 units, serum cholesterol 315 mgm. %, Random blood sugars on three occasions 360 mgm.%, 263 mgm. %, 336 mgm.%. Liver function: Thymol turbidity 1.5 units, thymol flocculation negative, Takata-Ara reaction (Ecko's modification) +++ positive. Alkaline phosphatase 32 units; van den Bergh reaction delayed direct, Bilirubin, direct 0.8 mgm.%, total 1.4 mgm. %. Icteric index 16. Prothrombin index 95%. Modified Ide test for Syphilis, negative. Urine analysis ++++ sugar, albumin nil, diastase 6.7 Wohlgemuth

/units...

units, Rous' test for iron, negative. Faeces analyses: No excess fats. X-ray Chest, heart and lungs normal. Electrocardiogram, Standard leads only, normal. Liver aspiration biopsy: Showed evidence of well marked iron deposition in parenchymal and Kupffer cells and in the portal tracts. There was a moderate degree of cirrhosis present with some bile duct hyperplasia.

Progress: In the first few days in hospital the patient required an average of 80 units insulin daily to control her diabetes. However, after approximately a week she became comatose; it was found to be hypoglycaemic and responded promptly to intravenous glucose. Subsequently she was started on a regime of 15 units Protamine Zinc insulin and 35 units of soluble insulin daily. On this therapy she gained weight and her appetite returned. She continued to show one to two pluses of sugar in the urine and the size of the liver did not diminish. She was finally discharged on this regime, but, unfortunately has not been seen since that time.

CASE 8, a Coloured female was aged 60 years when first seen in July, 1948. At the time she presented with a

/two ...

two week history of swelling of the abdomen. Appetite was good and bowels were usually regular. Her diet had been adequate, except for some deficiency of meat; for years she had been a heavy drinker of 'kaffir' beer.

Systematic and family histories did not seem to be contributory. She had 4 living children and the menopause had occurred uneventfully several years previously.

On Physical examination: The skin was dry and scaly with some increased pigmentation of the exposed parts. There was no anaemia. The teeth were carious but there was no pigmentation of the buccal mucous membrane. The pulse rate was 70 per minute and the blood pressure 140/80 mm.Hg. There was nothing abnormal in the cardio-vascular or respiratory systems. The abdomen was distended and there was a moderate amount of free fluid present. The liver edge was felt 4 fingers below the costal margin and was hard and irregular. The spleen was also palpable, being enlarged 2 fingers and very firm. There was calf tenderness with increased reflexes in the lower limbs.

Investigations were begun to elucidate the nature of the hepatomegaly.

/Laboratory ...

Laboratory Data Full blood count:- Haemoglobin 11.5 grams %; erythrocytes per cu.mm 4,220,000; leucocytes per cu.mm 7,400; polymorphs 40%; mononuclears 7%; lymphocytes 49%; eosinophils 4%; basophils 0%; Sedimentation rate (corrected) moderate increase. Blood proteins, 3.8 grams % albumin, 4.1 grams % globulin. Sugar tolerance (after 50 grams glucose by mouth) - fasting level 97 mgm.%, ½ hour 135 mgm.%, 1 hour 145 mgm.%, 1½ hours 135 mgm. %, 2 hours 113 mgm.%. Liver Function: Thymol turbidity 2 units, thymol flocculation one + positive. Takata-Ara reaction +++ positive; Total bilirubin less than 0.5 mgm. %. Icteric index 7 units; Alkaline phosphatase 11.2 King Armstrong units; Prothrombin index 63%. Urine Analysis: trace albumin, nil microscopically. X-ray Chest, some calcification of aortic knuckle. Nil else. Liver aspiration biopsy (after previous medication with vitamin K), excess iron deposits in parenchyma and portal tracts. Deposits heavier in portal tracts; definite thickening of portal tracts.

Progress: The patient's course in hospital was uneventful. She was treated conservatively on a high protein, high carbohydrate and low fat diet; on this regime the ascites disappeared and she gained weight.

/There ...

There was, however, no decrease in the size of the liver. She was finally discharged after 6 weeks in hospital.

Second Admission: She was readmitted to hospital 9 months after her previous discharge complaining of the recent onset of diarrhoea and swelling of the ankles. In addition, her appetite had become very poor in the preceding weeks.

The physical findings were very similar to those on the previous admission and the patient's symptoms were regarded as compatible with the degree of liver disease which was present. Therapy was again conservative. She responded well to dietary measures and was discharged after a month in hospital. A barium swallow on this admission showed no evidence of oesophageal varices.

Third Admission: Four months after her previous discharge the patient was readmitted. She was again complaining of loss of appetite and diarrhoea, but, in addition had noticed swelling of the abdomen and legs in the previous two weeks.

On Physical Examination: She was found to have gross

/ascites ...

ascites together with sacral oedema and oedema of the lower limbs. No further investigations were done and she was treated on a salt-free diet, vitamin supplements and liver injections. On this therapy the ascites and oedema disappeared and appetite returned. She was discharged after a month's stay in hospital.

Fourth Admission: The patient was readmitted in October, 1950, 4 months after having been discharged from hospital with a history of having vomited at least 4 cupfuls of bright red blood on the night prior to admission.

On Physical Examination: she was found to be very pale. There were, however, no signs of shock, the pulse being 98 and the blood pressure 116/65 mm.Hg. The rest of the findings were similar to those on her previous admission.

The haemoglobin was found to be 6.5 grams per cent and she was given 1000 ccs. blood intravenously. She was subsequently treated with a Meulengracht diet and there was no recurrence of bleeding. After 3 weeks of this therapy she was transferred from Baragwanath

/Hospital ...

Hospital to the Non-European Hospital where further laboratory tests and radioiron studies were carried out.

Additional Laboratory Data: Full blood count, Haemoglobin 10.5 grams%, erythrocytes per cu.mm. 3,550,000, leucocytes 7,300, polymorphs 66%, lymphocytes 25%, monocytes 4%, eosinophils 4%, basophils 1%. Blood proteins: 2.7 grams% albumin, 4.8 grams % globulin. Serum chlorides 585 mgm.%, blood urea 27 mgm. %, serum cholesterol 180 mgm. %, serum amylase 202 units. Sugar tolerance (After 50 grams glucose by mouth): fasting level 85 mgm.%, ½ hour 140 mgm. %, 1 hour 155 mgm. %, 1½ hours 125 mgm. %, 2 hours 115 mgm.%, Prothrombin index 63%. Modified Ide test for Syphilis, positive. Urine analysis: trace albumin, urobilin absent. Microscopically 3-5 polymorphs per spun high power field. Rous' test for iron, positive. Faeces (24 hour specimen) no excess fats. X-Ray Chest : No pathology in heart of lungs. Basal metabolic rate + 20%. Liver aspiration biopsy (after previous vitamin K medication). Cirrhosis of monolobular type with parenchymal and portal iron deposits. Skin biopsy, Considerable quantities of haemosiderin in the corium.

/Progress...

Progress: After the completion of the radioiron absorption investigations she was discharged from hospital. At the time she was feeling well and her haemoglobin had risen to 12.5 grams %.

Final Admission: The patient was readmitted in a collapsed bled-out condition two months after her previous discharge. She was stuporose and disorientated so that no history could be obtained. A blood transfusion was immediately started but there was no response and she died in coma within 24 hours of admission. A blood urea estimation shortly before death gave a result of 150 mgm. %.

Summary of Post Mortem Findings: There was nothing of note in the external appearances. There was some oedema of the lungs which showed a moderate degree of emphysema. The heart (weight 570 grams) was well coloured and the muscle firm. There was some degenerative thickening of the aortic cusps. There was pigmentation in the mucosa of the upper gut with many fine bleeding points in the stomach and intestine. here were no oesophagal varices. The liver (weight 2200 grams) was brown in colour with a finely nodular surface. The pancreas, which was firm and fibrotic, showed

/increased ...

increased pigmentation. There was some granularity of the surfaces of the kidneys. The spleen (weight 550 grams gave a positive Prussian blue reaction. The adrenals and thyroid were macroscopically normal. The brain showed no abnormality.

Microscopically: The liver showed a moderate amount of haemosiderin most of which was deposited in the portal tracts. There was a lesser amount of haemosiderin in the liver cells and in the Kupffer cells, some cells being much more affected than others. The portal tracts were definitely thickened and a monolobular type of cirrhosis was present. Sections of the pancreas showed gross post mortem change. There was a moderate amount of haemosiderin in the gland cells, and a small amount in the interstitial tissue. No islets were identified and no fibrosis was present. There was a moderate amount of haemosiderin in the phagocytic cells of the splenic pulp. Sections of the small intestine showed a brownish pigmentation of the mucosa mainly in the phagocytes. This pigment resembled haemosiderin on the haematoxylin and eosin sections but did not give a positive reaction with potassium ferrocyanide and hydrochloric acid, so that it may have been haemofuscin. An abdominal lymph node had marked deposits of iron-containing

/pigment ...

pigment in the follicles and small amounts in the capsule. The kidney showed no haemosiderin in the tubular cells or in the interstitial tissue. There were minute quantities of iron-containing pigment in the adrenals. They were present in the cells of the outer layer of the stratum granulosum just beneath the capsule. Sections of the ovary showed no haemosiderin. The thyroid was normal. There was no iron-containing pigment in the heart. Sections of the brain, including the pituitary, showed no haemosiderin.

CASE 9. was a coloured male who was aged 64 years when first seen in 1950. Unfortunately the records for this admission are not available so that the exact presentation is unknown. However it is known that he showed both glycosuria and hepatomegaly and it has been possible to locate the results of certain investigations done at the time.

Available Laboratory Data: Liver function: Thymol turbidity 5.5 units, thymol flocculation ++++ positive. Takata-Ara reaction (Ueko's modification) +++ positive. Sugar tolerance (after 50 grams glucose orally) - ½ hour 185 mgm.%, 1 hour 310 mgm. %, 1½ hours 321 mgm.% 2 hours 345 mgm. %, 3 hours 209 mgm. %, 4 hours 200 mgm. %.

/Liver ...

Liver aspiration biopsy: considerable increase of portal fibrous tissue leading to a multi-nodular cirrhosis. In addition, considerable iron deposits present in the parenchymal and Kupffer cells and the portal tracts.

Progress: He was regarded as a case of cytosiderosis with diabetes and was treated with dietary measures and with insulin. He was finally discharged on a maintenance dose of insulin but the exact amount is not known.

Second Admission: The patient was readmitted in September, 1951 for radioiron studies. At the time he was in good health and had no complaints. He did not require any insulin.

The only points of interest in the systematic history were that he had been treated in 1924 and 1950 for Syphilis at Rietfontein Hospital. There had also been a short stay at the Pretoria Mental Asylum in 1924 but the reason for this was not known. The diet had always been poor in proteins, with only one meat-containing meal per week. He had also consumed a daily quantity of approximately 2 jars of 'kaffir' beer for many years.

/On ...

On Physical Examination: He was well preserved for his age. There was no abnormal pigmentation of the face but there was excessive pigmentation over the exposed parts of the arms and legs. The parotids were slightly enlarged. The borders of the tongue and the roof of the hard palate had a bluish-grey colour and the teeth were carious. The thyroid was not palpable. The pulse rate was 60 per minute and the blood pressure 140/90 mm.Hg. The heart was not clinically enlarged. On auscultation a soft blowing systolic murmur could be heard down the left sternal border. The respiratory system was normal. The liver was enlarged four fingers below the costal margin, the edge being firm, non-tender and irregular. The tip of the spleen was just palpable. There was no testicular atrophy. The central nervous system was apparently normal.

Additional Laboratory Data: Full blood count - Haemoglobin 15.6 grams %, erythrocytes per cu.mm. 5,280,000, leucocytes per cu.mm. 6,[illegible]00, neutrophils 50%, monocytes 6%, lymphocytes 41%, eosinophils 2%, basophils 1%. Sedimentation rate 7 mm. in 1 hour. Serum cholesterol 90 mgm. %, serum amylase 150 units, blood calcium 9.3 mgm.%. Sugar tolerance (after 50 grams glucose by mouth). Fasting level 102 mgm.%,

/½ hour ...

½ hour 120 mgm. %, 1 hour 152 mgm.%, 1½ hours 156 mgm. %, 2 hours 146 mgm. %, 2½ hours 116 mgm.%. Liver Function: Thymol turbidity 6 units, thymol flocculation ++++ positive, Takata-Ara reaction (Loko's modification) ++++ positive. Alkaline phosphatase 32 King-Armstrong units; bilirubin: direct 1.6 mgm.%, total 2.0 mgm.%, Icteric Index 16, Prothrombin index 91%, Kahn test for Syphilis positive. Urine analysis, nil chemically and microscopically, Faeces analysis no excess fats. X-Ray Chest, the heart showed a hypertensive configuration. Electrocardiogram, normal.

Progress: He was completely asymptomatic while in hospital and in the three months period during which he was followed up after discharge.

Third Admission: He was readmitted to hospital in March, 1952, 4 months after his previous discharge. He had been well until 1 month before admission when he suddenly vomited up 2 pints of dark red blood. Since that time he had suffered from intermittent bouts of colicky abdominal pain with some diarrhoea and tenesmus.

On Physical Examination: The findings were similar to those on his previous admission. However, on testing

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his urine it was found that the glycosuria had retuned and he was started again on insulin therapy. In addition a sigmoidoscopy revealed ulceration of the bowel and vegetative forms of entamoeba histolytica were found on smears taken from the ulcer craters.

He was treated with aureomycin and emetine with good result and he was finally discharged on a maintenance schedule of 25 units Protamine Zinc insulin and 15 units soluble insulin daily.

Final Admission: The patient was readmitted in October, 1952, 6 months after his last admission. He had remained in good health until 3 days previously when he had suddenly developed an acute pain in the chest and bladder while having a cold shower. This had been followed by persistent vomiting and swelling of the abdomen.

On Physical examination: He was found to be dyspnoeic and cyanosed. There was no icterus. The pulse rate was 100 per minute and the blood pressure 130/68 mm.Hg. There were no signs of congestive cardiac failure but a gallop rhythm was heard at the apex of the heart which

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was clinically enlarged to the left. The lung fields were clear except for a few scattered fine crepitations at the bases. The liver was enlarged 3 fingers below the costal margin being firm and non-tender and the spleen was also felt two fingers below the costal margin. No reflexes could be elicited in the central nervous system and both plantar responses were flexor.

Progress: In the following hours he became progressively more drowsy. There was almost no urinary output; the specimens which were passed showed ± 5 red cells per high power centrifuged field with occasional granular casts. There was no albumin. A blood sugar estimation gave a result of 158 mgm.% and the blood urea was 87 mgm.%. The exact nature of this terminal episode was not clear. He was treated with penicillin and oxygen and with intravenous therapy. In spite of therapy he became progressively more shocked and died in coma within 24 hours of admission.

Summary of Post Mortem Findings: The body was fairly well nourished. There was early clubbing of the fingers. The lungs showed basal lobe atelectasis with congestion. There was some brownish pigmentation of the heart which weighed 400 grams and the ascending aorta was dilated.

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There were no oesophageal varices. The stomach showed evidence of hypertrophic gastritis and the mesenteric lymph glands were pigmented. There was an early peritonitis of the serosal surface of the upper jejunum. The liver (weight 3170 grams) was coarsely fibrotic and was brown in colour. The pancreas was atrophic and showed brownish pigmentation. There was swelling of both the cortex and medulla of the kidneys. The spleen (weight 760 grams) showed an acute perisplenitis and gave a positive Prussian blue reaction for iron. The thyroid also gave a positive Prussian blue reaction. The brain was apparently normal.

Microscopically: The liver showed well marked diffuse hepatic fibrosis. There was a moderate deposit of haemosiderin in the liver cells, Kupffer cells and fibrous tissue. There was a moderate degree of interlobular fibrosis of the pancreas with some iron-containing pigment in the fibrous tissue and slight deposits in the parenchymal cells. Very slight deposits were also present in the islets of Langerhans. Sections of the intestine showed no evidence of iron deposits. There was well marked congestion of the spleen with moderate deposits of haemosiderin. Sections of the heart showed a well marked increase in lipoidal pigmentation and

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slight deposits of haemosiderin were present in some of the fibres. This was very focal as other sections showed no signs of iron deposition. There was no haemosiderin in the lungs, kidneys and skin. In the thyroid, however, there were moderate deposits of haemosiderin in the colloid secretion and in the epithelial cells.

CASE 10 , was a Bantu female, aged ± 66 years who presented first in May, 1948 with a history of pain in the right hypochondrium for 3 years. During this period she had also had a non-productive cough, but this had not been particularly troublesome. Appetite had always been good but in the two months prior to admission there had been some weight loss. She had been on a diet deficient in proteins and had taken regular moderate quantities of 'kaffir' beer.

On Physical Examination: She was poorly nourished with deep pigmentation of the skin of the exposed parts. The tongue was smooth and there was no pigmentation of the mouth. The radial pulse was 78, the rhythm regular and the vessel was thickened. The blood pressure was 170/110 mm.Hg. but no other abnormality of the cardio-vascular system was noted. The lung fields were clear.

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The liver was enlarged 4 fingers below the costal margin, the edge being hard, non-tender and somewhat irregular. There was no peripheral neuritis.

A diagnosis of cirrhosis of the liver was considered and laboratory tests were carried out from this point of view.

Laboratory Data: Full blood count: Haemoglobin 15.5 grams %, erythrocytes per cu.mm. 5,000,000. leucocytes per cu.mm 6,8000, neutrophils 51%, monocytes 9%, lymphocytes 33%, eosinophils 4 %, basophils 3%, Blood proteins: 2.9 grams % albumin, 2.9 grams % globulin. Liver function: Thymol turbidity 6 units, thymol flocculation ++ positive. Takata-Ara reaction ++ positive. Icteric index 16 units. Alkaline phosphatase 10.3 King-Armstrong units. Prothrombin index 81%, Urine analysis nil chemically and microscopically. X-ray chest, heart and lungs normal. Liver aspiration biopsy: a marked degree of cirrhosis was present with heavy deposits of haemosiderin in the fibrous tissue. Lesser quantities were found in the Kupffer cells while deposits in parenchymal cells were relatively slight.

Progress: The patient was treated conservatively on a high protein diet with vitamin supplements and was well

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enough to be discharged after two weeks in hospital.

Second Admission : She was not seen for three years but was finally brought back to hospital by her son because of the onset of generalised convulsions. According to him she had been well until two months previously. Then, she started having convulsions which appeared to be epileptiform in type. In all she had had about six such attacks. In addition he had noted that she was becoming progressively more weak. Appetite throughout had been good, although her diet, as on the previous admission was poor. According to her son she was a heavy brandy and 'kaffir' beer drinker. She had three living children; 5 others had died in early childhood.

On Physical Examination: She was found to be uncooperative but not disorientated. There was some wastin and a generalised loss of body hair. There was deep pigmentation with some scaling of the exposed parts. There was no jaundice or anaemia. The teeth were carious and the tongue smooth but no abnormal pigmentation in the mouth could be seen. She was aprexial, the pulse rate was 106 and the rhythm normal. The

/blood ..

blood pressure was 160/110 mm.Hg. No abnormalities of the cardiovascular and respiratory systems were detectable. The liver was enlarged 4 fingers below the costal margin and had a firm non-tender edge. There was no splenomegaly or ascites. In the central nervous system the only abnormality noted was an irregular twitching of the right arm. Power was good, reflexes equal and the plantar responses flexor.

A diagnosis of malnutritional cytosiderosis with a superimposed Wernicke's encephalopathy was made.

Laboratory Data: Full blood count: Haemoglobin 16.9 grams %, erythrocytes per cu.mm. 5,690,000, leucocytes per c .mm. 6,200, polymorphs 67%, monocytes 6%, lymphocytes 24%, eosiniphils 2 , basophils 1%. Sedimentation rate: 7 mm. in 1 hour. Blood proteins 2.7 grams %. Albumin 3.1 grams % globulin. Blood urea 23 mgm. %. Serum amylase 70 units. Sugar tolerance (after 50 grams glucose by mouth). Fasting level 60 mgm. %, ½ hour 65 mgm.%, 1 hour 85 mgm. %, 1½ hours 115 mgm.%, 2 hours 100 mgm.%, 2½ hours 75 mgm. %. Liver Function: Thymol turbidity 3.5 units, thymol flocculation ++++ positive, cephalin cholesterol ++++ positve, Takata-Ara (Ucko's modific tion) +++ positive. Prothrombin Index 91%. Modified Ide

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test for Syphilis, positive. Urine Analysis, nil chemically and microscopically. Cerebrospinal fluid:- Cell count: 2 polymorphs, 45 erythrocytes. Total protein 56 mgm.%, chlorides 665 mgm.%, sugar 78 mgm.%, Lange's colloidal gold test, negative.

Progress: The patient was treated on a high protein diet and was given injections of Vitamin B complex and nicotinamide. On this therapy there was some improvement in her general condition. During this period radioiron absorption studies were performed on her.

However, after several weeks she became gradually more lethargic and she finally died in coma about five weeks after admission.

Summary of Post Mortem Findings: There was generalised wasting with atrophy of the skin. There was diminution of all the body hair. Both lungs showed oedema. The heart (weight 200 grams) was not enlarged, the muscles being flabby and brown in colour. There was atheroma of the aortic arch. There was marked postmortem change of the gut but no other abnormalities were noted. The liver (weight 1580 grams) was brown in colour and showed evidence of both coarse and fine nodularity. The pancreas

/which ...

which was pigmented, was firm and fibrotic. The spleen was moderately enlarged (weight 240 grams) and there was some perisplenitis. The kidneys appeared normal and the suprarenals showed autolytic changes. The thyroid was grossly atrophic. The brain showed atrophy of the cortex and on section seemed normal.

Microscopically: Sections of the liver showed marked cirrhosis resembling that secondary to post necrotic scarring. Very heavy deposits of haemosiderin were present in the fibrous tissue and a moderate amount was present in the Kupffer cells, while a slight amount was found in the liver cells. The pancreas showed marked chronic pancreatitis, both perilobular and periacinar in distribution. The pancreatic ducts were dilated and contained calculi. There was a large amount of iron pigment in the fibrous tissue and a moderate amount in the glandular cells. Post mortem necrosis was marked and no definite islet tissue could be identified. There was no evidence of haemosiderin in the gut. Sections of the spleen showed a very heavy deposition of haemosiderin in the pulp, both intra and extracellularly. Small amounts were present in the follicles. The heart had heavy deposits of haemosiderin in the muscle fibres.

Not all were affected, the amount varying from fibre to fibre. Some of the muscle fibres were atrophic; a small amount of iron pigment was also present in the interstitial tissue. Haemosiderin was also present throughout the coats of some of the arteries. Sections of the lung showed small quantities of haemosiderin in some of the alveoli and, in addition, there was con estion and oedema. The haemosiderin was probably associated with red cell breakdown. There was chronic non-specific thyroiditis, masses of haemosiderin being present in the cells lining the acini and in the colloid, although not all the acini were affected. There was much less haemosiderin in the gland tissue than in the fibrosis tissue. Clumps of iron pigment were seen in some of the veins. There was no evidence of iron deposition in the brain.

D I S C U S S I O N.

In the discussion which follows it is proposed to review what is known of the clinical and pathological findings in malnutritional cytosiderosis. In addition the patho enesis is discussed with special reference to the views of others and to the results of the present investigation.

CLINICAL PRESENTATION:

Unfortunately little evidence is available as to the clinical findings in malnutritional cytosiderosis. The Gillmans' studies which were primarily histological ones (8),(9),(10),(11), drew attention to the high incidence of the condition in Bantu pellagrins. Higginson and co-workers' investigation (16) was a mor id anatomical, histopathological and chemical one but they did attempt to correlate their results with the clinical data of each case and were thus able to compare to some extent the presentation with that seen in idiopathic haemochromatosis.

They found that there was no very clear cut sex incidence there being 178 males and 118 females in their series. No special age incidence was noted; however the severity tended to be reater in older age groups.

There was no correlation between the nutritional state and the degree of siderosis in viscera and a typical pellagroid rash was found in only two cases. Increased pigmentation of the skin was commonly seen but was due to melanin in most cases and was unrelated to the amount of haemosiderin in the abdominal organs. In a few severe cases, however, microscopic examination of the skin showed a few scattered haemosiderin granules in the corium, most marked in the skin appendages. Diabetes mellitus was present in only 3 of 296 cases. Endocrine changes, as judged by testicular atrophy and gynecomastia, were present in several cases but no correlation with the degree of visceral siderosis or hepatic cirrhosis could be established. Hepatomegaly as a clinical feature was not commented upon. The primary cause of death varied widely and did not seem to be related to the severity of siderosis. The commonest cause was 'cardiovascular disease' (106 cases) while cirrhosis of the liver was only regarded as a casual factor in 4 subjects.

On this evidence there would seem to be little similarity between the clinical presentation in malnutritional cytosiderosis and idiopathic haemochromatosis. There was a striking difference in sex incidence. In addition, skin pigmentation due to iron

deposits ...

deposits, which is found in at least 50% of cases of idiopathic haemochromatosis, and diabetes, which is present in 75%, were rare. Cirrhosis of the liver which is almost invariably found in idiopathic haemochromatosis was present in only a quarter of the severe cases and endocrine changes were infrequent. However, it should be remembered that the diagnosis of idiopathic haemochromatosis can only be made in the terminal phases of the condition when the pathological process has already been present for many years. It is therefore not completely valid to compare the findings in cases of malnutritional cytosiderosis of all grades of severity with those in idiopathic haemochromatosis. Such an explanation may in part at least, account for some of the discrepancies between these reported comparative findings.

The clinical findings in the 5 cases studied in this paper are in some contrast to those of Higginson and co-workers. In each of these cases there was a history of a diet deficient by European standards, and in addition, each admitted to a heavy consumption of 'kaffir' beer over many years. There were two males and three females the average age being 59 years (range 47 to 66).

/Skin ...

Skin pigmentation, more marked on the exposed parts, was present in all cases and was associated with excessive iron deposits in the two cases in which skin biopsies were taken. Diabetes mellitus, severe enough to require insulin therapy, was present in 3 cases and was confirmed in each case by glucose tolerance curves. An interesting feature in two of these cases was the return of a normal sugar tolerance spontaneously after several months. In one of these glycosuria returned subsequently and further insulin therapy was required. Hepatomegaly was invariably found and liver aspiration biopsy showed evidence of cirrhosis with heavy iron deposits in all cases. Endocrine changes were not present in any subject. The cause of death in two cases seemed to be related to hepatic failure while it followed on a haematemesis, secondary to widespread intestinal haemorrhage, in a third. The other two cases were still alive when last seen.

On the present clinical data there were therefore definite similarities between the clinical presentations in idiopathic haemochromatosis and malnutritional cytosiderosis. However, these cases were, to some extent, artificially selected in so far as the presence of diabetes together with hepatomegaly in 3 of the cases was used as

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the indication for the liver aspiration biopsies on which diagnosis was made. Higginson and co-workers have shown that visceral siderosis may be found at autopsy together with a wide variety of unrelated pathological conditions so that the co-existence of diabetes and cytosiderosis may have been coincidental in the present cases. In spite of this qualification and the fact that the present series is a small one, the similarites in presentation between the two conditions under review were close enough to be suggestive. The results also seem to underline the need for more comparative clinical studies to be done at comparable stages in malnutritional cytosiderosis and idiopathic haemochromatosis. To achieve this would require the more widespread use of liver aspiration biopsies in suspected cases of malnutritional cytosiderosis in order to confirm the presence of cirrhosis together with hepatic siderosis.

PATHOLOGICAL FINDINGS:

The Gillmans' (8),(9),(10),(12), in their description of the histological findings in the liver in malnutritional cytosiderosis, divided the findings into several stages. In the first stage fine granules of iron-containing pigment were found in the hepatic

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epithelium. In the second stage the quantity of iron in the liver cells either decreased or increased but whatever iron was present, tended to aggregate in clumps. In addition, iron pigment now appeared in the Kupffer cells and in the portal phagocytes. In either of these stages varying degrees of fatty change might occur. In the third stage, fibrosis was superimposed on the earlier pictures and histological features indistinguishable from those described in idiopathic haemochromatosis were often obtained. Unfortunately these authors did not describe in detail the histological findings in other organs but included micro-photographs in a publication (12), showing widespread deposits of iron-containing pigment in the pancreas, bowel, thyroid, lymph glands, spleen, striated muscle and heart. Thus findings in the later stages of malnutritional cytosiderosis, very similar to those in idiopathic haemochromatosis were present and these authors considered the two conditions to be closely allied. The actual pathogenesis which they profounded in view of their histological studies will be described in a later section.

The other available evidence of the pathological findings in malnutritional cytosiderosis is that provided recently by Higginson and co-workers (16).

/This ...

This later investigation included a careful morbid anatomical examination of most of the viscera together with histological studies and chemical assays. The livers with a moderate degree of siderosis had a rusty colour and gave a positive Potassium Ferrocyanide reaction. In some cases iron-containing pigment was present in both parenchymal and Kupffer cells. In some cases it was only present in parenchymal cells and in others only in Kupffer cells and there seemed to be no correlation between the degree of deposition in the two sites. In siderotic cases of all degrees of severity, deposits of iron were also noted in the portal tracts. While there was a tendency for severe siderosis to be associated with portal fibrosis and cirrhosis some cases with heavy iron storage showed little or no fibrosis. The spleen usually had a markedly rusty colour and showed, on microscopic section a much greater concentration of iron than the liver. This was mostly located in the endothelial cells and macrophages. In the pancreas, however, only slight deposition of haemosiderin was present and only 7 of 82 examined showed evidence of iron pigment in the acinae and islets. In some, a fine interstitial fibrosis was present. The heart only rarely showed any iron pigment and of the 21 cases with severe hepatic siderosis only 4 showed any

/iron ...

iron granules in the myocardial fibres. The kidney in severe or moderate cases showed scanty haemosiderin granules. In the gastro-intestinal tract the outstanding findings were noted in the duodenum and jejunum. In cases with moderate or severe hepatic deposits the mucosa was rusty in colour and on microscopy iron-containing macrophages were found in the substantia propia of the villi. In severe cases all cellular detail in the villi was obscured by intra and extracellular pigment. The lymph nodes draining the upper bowel were shown to have heavy iron deposits while those draining the ileum and colon had little or none. Sections of the thyroid, pituitary and testes showed only a few scattered haemosiderin-containing macrophages in the interstitial tissue.

The pathological findings in malnutritional cytosiderosis therefore showed several distinct differences from those in idiopathic haemochromatosis. The striking differences were the heavy deposits in the spleen, the absence of pancreatic pigmentation in most cases and of significant haemosiderin deposits in the epithelial elements of the stomach, thyroid, salivary glands, suprarenals and myocardium. In addition the massive deposits of iron which were found in the jejunal

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and duodenal mucosa are not a feature of idiopathic haemochromatosis (25). The differences found on histolo ical examination were also confirmed by chemical analysis of organs, the figures being compared with those described by Sheldon (25) in idiopathic haemochromatosis.

In the present series three of the cases investi ated died subsequently and had autopsy examinations performed on them. The pathological findings were very similar to those described by Hi ginson and co-workers (16). However, in cases 9 and 10 there was no evidence of haemosiderin deposits in the bowel. In addition case 10 showed moderate amounts of iron pigment in glandular organs and heavy deposits in heart muscle giving a post mortem histological picture v ry similar to that in idiopathic hae ochromatosis.

PATHOGENESIS OF MALNUTRITIONAL CYTOSIDEROSIS

Views on pathogenesis of the condition based on histopathological and other findin s are somewhat conflicting. The Gillmans (12), on the ore hand, regard it as a profound metabolic upset closely related to idiopathic haemochromatosis but initiated by chronic malnutrition. Higginson and co-workers (16), however, feel that it is probably a different pathological

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entity affecting primarily the reticulo-endothelial system. These two views are worthy of a separate and more detailed analysis.

As their studies showed only parenchymal deposits of iron in the livers of early cases of alnutritional cytosiderosis the Gillmans postulated that the initial derangement in the disease is one of intracellular metabolism which is precipitated by prolonged malnutrition. They produced evidence to support the contention that this iron is derived from mitochondrial breakdown. Some of this iron pigment is then excreted into the bowel and re-absorbed. At this stage it is probable that the alimentary mucosal block becomes deranged and this leads to further iron absorption. This derangement, they considered, as possibly due in part to pancreatic damage and also to a stimulation of the reticulo-endothelial system by some metabolic derangement. During this second stage of the disease, excessive quantities of iron are absorbed from the gut and the reticulo-endothelial system becomes loaded with an iron-protein complex. They considered that such a sequence of events may also occur in idiopathic haemochromatosis although the initial metabolic dyscrasia in this disease is an inherited one and is not secondary to malnutrition.

/Unlike ...

Unlike the Gillmans, Higginson and co-workers (18) found that iron deposition was widespread in the reticulo-endothelial system from the beginning and the pathological features, though having similarities to those in idiopathic haemochromatosis, showed also definite differences. At all stages of the condition the reticulo-endothelial system showed much heavier deposits than did epithelial tissues. The spleen always showed greater concentrations of iron than the liver in contrast to idiopathic haemochromatosis, where only relatively slight amounts are present in the spleen while deposits in organs such as the pancreas, heart, thyroid and adrenals were scanty or absent. In addition, they could not demonstrate any casual relationship between the presence of malnutrition and the degree of siderosis. They, therefore, postulated that the condition was possibly related to the fact that these subjects, who have been shown to have very high quantities of iron in their diets (29), (30), absorb and deposit more iron than do normals. They could not relate these iron deposits to the primary cause of death and doubted whether the condition of malnutritional cytosiderosis actually represents a disease entity.

From the summaries of these two widely differing

/views ...

views on pathogenesis it is clear that no definite answer to the problem of malnutritional cytosiderosis has yet been reached. Both groups of workers, however, agr ed that the source of the iron deposits must be from the gut as excessive haemolysis has been shown to be definitely not a significant factor (8). It was to study in more detail the pattern of iron absorption that radioiron studies were carried out on the 5 cases of malnutritional cytosiderosis described in this thesis.

The absorption of iron from the bowel in 4 of these s bjects seemed to be very little as there were low blood levels and no evidence of visceral deposition as judged by in vivo counts over body organs. In the 5th case (No.9) a blood uptake which fell into the normal ran e w s obtained and there also seemed to be some deposition of radioiron in the liver. He was the only one of the 5 who was examined while on his usual diet, the others having spent periods of up to several weeks in hospital prior to being studied. There was, therefore, a definite difference in iron absorption between those patients who were on hospital ward diets and the one case who still was on his usual 'Bantu' diet. To analyse the possible significance of this discrepancy it is necessary to review what is known of the influence

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of dietary changes in iron absorption.

Kinney (19) has shown that rats fed on a deficient corn grit diet supplemented with iron develop a marked siderosis of body organs, the distribution being similar to that described by Higginson and co-workers (16) in malnutritional cytosiderosis. They have also found that such a siderosis may be prevented if phosphate is added to the diet (19). In addition, Taylor and co-workers (27) have shown that depancreatised cats develop a siderosis. They have also produced the same finding by ligating the pancreatic ducts but have been able to prevent much of the increased absorption by the addition of haliverol to the cats' diet (28). More recently Cartwright and co-workers (5) have also produced increased iron absorption in animals with a diet deficient in pyrodoxin. It is therefore possible that such factors as pancreatic damage and deficiencies of phosphates, fat soluble vitamins and pyridoxin may potentially affect iron absorption in human subjects.

Pancreatic damage was presumed to be present in 3 of the cases of malnutritional cytosiderosis who were investigated in the present study as each had diabetes mellitus. In two of them, however, the absorption of radioiron was very low so that it is difficult to relate absorption to such a factor. This view is supported in

/some ...

some measure by Higginson and co-workers (16) who found that the majority of the 82 pancreases which they examined were microscopically normal. It is, however, possible, though unlikely, that some pancreatic defect may still be present in such cases in spite of normal histological findings. The role of phosphates, fat soluble vitamins and pyridoxin in the etiology of malnutritional cytosiderosis is not clear. The phosphate content of the 'Bantu' diet (30) is high and fat soluble vitamins do not seem to be grossly deficient (31). Little is known of the role of pyridoxin in human metabolism and at present no clinical syndrome has been linked with such a deficiency (18). There is, therefore, no specific deficiency which can be incriminated at the moment as an etiological factor in malnutritional cytosiderosis.

The question therefore arises as to whether malnutrition itself is necessary in the development of the condition. It is noteworthy that cytosiderosis has not been reported from other parts of the world where malnutrition is common (30). A factor, however, which seems to be peculiar to the local Bantu population is the preparation of food and fermented beer in iron cooking pots. In has recently been shown that this leads to a

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daily intake of iron in these people which is usually over 100 mgms. and may be as much as 200 mgms. (29). Investigations done on human volunteers have shown that when large quantities of iron are given by mouth over long periods the percentage absorbed is less. This is due to the presence of a normal mucosal block to excessive iron absorption (14). However, this block is not as complete as had been previously postulated (6) with the result that the absolute quantity of iron retained in the body may be much greater than normal when large amounts are given by mouth. This is especially true when hypochromic anaemia is present as it has been shown that under such circumstances as much as 8.85 grams may be retained over a period of 24 days. However, even in normal subjects appreciable quantities of iron may be retained in the body if large amounts are fed by mouth (2), (7),(13), (32). In one such experiment conducted over 36 days Widdowson and McCance (32) showed a retention of over 5 grams, and later radioiron studies (6) have confirmed that the 'mucosal block' is by no means an absolute one.

It, therefore, seems possible that Bantu subjects with excessive iron in their diets may absorb and deposit large quantities in their bodies over long periods and

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that this increased absorption is not necessarily related to malnutrition. However, the fact remains that these subjects subsist on a diet which is inadequate according to European standards. It is therefore still possible that some deficiency, as yet undefined may play a part in allowing for a relatively excessive absorption of iron from the bowel. Such a contention is supported to some extent by the fact that the greatest degree of iron absorption in the present study was recorded in the one case who was still on his natural deficient diet.

Although a dietary deficiency is a possible explanation for such a finding it is, theoretically at least, not the only one. The presence of a toxic agent in such diets, has not been excluded. Mallory (20),(21) has produced experimentally a siderosis by chronic copper poisoning and has even suggested that this might be the cause of idiopathic haemochromatosis. (22). Although this claim has not been substantiated in this disease (23) the relationship of excessive copper intake to malnutritional cytosiderosis has not been investigated. One fact, however, which is known is that heavily pigmented livers in this condition have also increased copper contents (11) and further study of this aspect seems worth while.

An important fact which did emerge from the

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present study was that none of the 4 subjects investigated while on hospital diets exhibited a pattern of iron absorption and deposition which resembled the findings in idiopathic haemochromatosis in any way. The Gillmans' contention that chronic malnutrition initiates a chain of events similar to that in idiopathic haemochromatosis is therefore not valid. It is possible, however, that progress of the condition may be halted if dietary deficiencies are rectified. Slight support for s ch a contention was the finding of an absorptive pattern in case 9, who was still on his usual deficient diet, which resembled to some extent that in idiop thic haemochromatosis as he was the only one to show evidence of significant iron deposition in the liver as shown by in vivo counts. nfortunately it was not possible to judge the exact quantity of iron retained in the body of this case owing to difficulties in faecal collections. The fact that he showed a significant dose of the administered radioiron circulating in his blood with evidence of organ deposition suggests that absorption may have been relatively high. When this is coupled with the fact that the radioiron was added to a diet which presumably already had a hi h proportion of iron in it, the possibility arises

/that ...

that the actual percentage absorbed may have been higher than normal, i.e. some intestinal mucosal defect was also present. However, this is conjecture and the differences found between the 4 hospitalised cases and this last subject may have been coincidental. It can be argued that these former subjects were in a later stage of the condition when it has already limited itself while the latter one was examined while still in an active phase. The heavy blockading of gut cells with iron in the condition may well indicate that it is to some extent self limiting and Becker (1) has gone so far as to suggest that the malnutrition in these cases may not be primary but secondary to interference with absorption of nutrients, caused by the heavy deposition of iron pigment in the intestinal cells. On available evidence therefore, no definite answer can be given to the possible role of a defective 'mucosal block' in malnutritional cytosiderosis, and the need for further absorption studies with patients on their natural diets seems indicated. Only when this has been done can the relationship of malnutritional cytosiderosis to idiopathic haemochromatosis be more clearly defined.

Whatever the exact relationship between these two conditions is, the fact remains that large quantities of iron accumulate in the body in malnutritional cytosiderosis

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and the question arises as to whether these deposits are deleterious to normal bodily function. Animal experiments, (3), (23), (24) as has been previously discussed, have not shown that such deposits are per se harmful, although these experiments have had a relatively short follow up. In addition neither were the Gillmans (12) nor Higginson and co-workers (16) able to relate the cirrhosis of the liver which occurs in the later stages to the degree of iron deposits. The primary cause of death in Higginson's cases also seemed to be unrelated to visceral iron deposits. This, however, does not necessarily mean that iron deposits may not indirectly lead to secondary pathology. Hueper (17) has produced experimentally, widespread systemic changes by injecting large inert molecules, such as polyvinyl alcohol, into laboratory animals. These included alterations in the blood, fibrosis of the spleen and atherosclerotic lesions. On this basis the Gillmans have suggested that widespread pathological changes may be induced by the flooding of the circulation with large relatively inert molecules, formed by the combination of iron with protein (11). They feel that the deposition of this iron throughout the reticulo-endothelial system may lead to a partial blockade of this system and that

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changes secondary to interference with reticulo-endothelial activity may then occur. Some support for this view has been given by the Gillmans' experiments with the macromolecule formed by the combination of injected trypan blue with plasma albumin. With this dye they have produced in rats cirrhosis of the liver, reticuloses, blood dyscrasias, sexual changes, arthritides and a wide variety of cardiac lesions. (12). In addition Cannon and McClelland (4) found that when the reticulo-endothelial system of Bartonella-infected rats is adequately blockaded with india ink, anaemia develops. Although it is not possible to relate such evidence directly to the problem of malnutritional cytosiderosis it seems of enough interest to allow for some caution to be exercised before dismissing the iron deposits in this condition as inconsequential.

/SUMMARY ...

SUMMARY AND CONCLUSIONS

(1) Detailed clinical data on 5 cases of malnutritional cytosiderosis are presented. In addition the clinical and pathological findings described by other authors and those found in the present investigations are discussed.

(2) Similarities between the clinical presentations in this condition and that in idiopathic haemochromatosis was found in this study although this has not been the experience of others.

(3) The pathological findings have definite differences to those in idiopathic haemochromatosis, the most striking ones being the large concentrations of iron in the spleen and upper intestine with relatively little in the heart and in epithelial tissues such as the pancreas.

(4) The pathogenesis of malnutritional cytosiderosis is still in doubt. There is, however, suggestive evidence that it occurs secondary to the ingestion of large quantities of iron in the Bantu diet and that it involves primarily the reticulo-endothelial system. The role of deficiencies or toxic agents in the diet which may allow for increased iron absorption from the bowel has not yet been defined.

/(5) ...

(5) Radioiron absorption studies in 4 subjects on hospital diets showed very low uptakes in the blood in each case, giving a pattern completely unlike that found in idiopathic haemochromatosis. Findings somewhat similar to those in idiopathic haemochromatosis were found in a fifth subject examined while still on his natural diet.

(6) There is no direct evidence that the iron deposits in malnutritional cytosiderosis are detrimental to the body although it is possible that irritation or blockading of the reticulo-endothelial system with iron may lead to secondary pathology.

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C H A P T E R IV.

THE RELATIONSHIP OF TRANSFUSIONAL HAEMOSIDEROSIS TO IDIOPATHIC HAEMOCHROMATOSIS.

There is a group of anaemias in which the haemoglobin level can be maintained only by the administration of repeated blood transfusions over long periods. The iron liberated from the breakdown of transfused blood is taken up initially by the reticulo-endothelial system, but as the quantity in the body increases, there is an overflow of iron into parenchymal tissues. In this way pathological findings very similar to those in idiopathic haemochromatosis may be found. There is controversy, however, as to the exact relationship between this transfusional haemosiderosis and idiopathic haemochromatosis, some authors considering them to be closely allied (20), (27), while others feel they are separate entities (24),(25). Any evaluation of the mechanism of transfusional haemosiderosis is also made more difficult by the fact that a proportion of such cases have shown more iron in the liver alone at autopsy than had been present in all the transfusions administered. It has therefore been suggested that iron derived from intestinal absorption may also contribute to the deposits throughout the body (24),(25).

In the present section the clinical data of three

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additional cases of transfusional haemosiderosis are presented. In addition, the findings in cases of transfusional haemosiderosis reported in the literature have been reassessed in an attempt to define more clearly its relationship to idiopathic haemochromatosis. The clinical presentation, pathological findings and pattern of iron metabolism in the two conditions are compared with special reference to findings reported elsewhere and to the results of the radioiron studies which were done in the present investigation.

CLINICAL MATERIAL (GROUP III)

CASE 11. a male aged 44 years, had received over 150 blood transfusions when he was admitted to hospital for radioiron studies in November, 1950. He had developed enlarged glands in the neck, axillae and groins 5 years previously and a diagnosis of chronic lymphatic leukaemia had been made on a series of blood counts taken at the time. He was treated with radiation therapy and remained in good health until two years later when he became listless and tired. A course of P^{32} was then instituted with no benefit and he became progressively more anaemic. A diagnosis of aplasia of the bone marrow was subsequently made and regular blood

/transfusions ...

transfusions were given. In the following three years he received more than 150 pints of blood and remained in good health.

On Physical Examination in November, 1950 there was a slaty grey pigmentation of the skin on the face and arms. He was mildly anaemic. The blood pressure was 104/70 mm.Hg. and the cardiovascular and respiratory systems were apparently normal. The liver was three fingers enlarged below the costal margin and the edge was firm and non-tender but there was no splenomegaly. There was a moderate non-tender enlargement of the cervical, axillary and inguinal lymph glands. He showed early gynaecomastia but hair distribution was normal and there was no testicular atrophy.

Laboratory Data: (After more than 150 pints of blood) Blood count: Haemoglobin 10.1 grams %, erythrocytes per c.mm. 3,750,000, leucocytes per c.mm. 13,500, neutrophil 11.5 %, monocytes 6.5 %, lymphocytes 80%, eosinophils 0%, basophils 0%, lymphoblasts 2.0%. Sedimentation rate (corrected): moderate increase. Modified Ide test for Syphilis: negative, Urine analysis: nil chemically and microscopically. Liver Function:

/Thymol ...

Thymol turbidity 5.5 units, thymol flocculation ++++ positive, Takata-Ara (Ucko's modification) negative, Icteric index 11 units. Prothrombin index 90%. Blood proteins: 3.7 grams % albumin, 3.4 grams % globulin, Sugar tolerance (after 50 grams per cent glucose orally): fasting level 85 mgm.%, ½ hour 100 mgm.% , 1 hour 135 mgm.%, 1½ hours 115 mgm.%, 2 hours 90 mgm.%, Serum and urinary diastase: normal. Fats in stool: no excess. X-ray of chest: heart normal; prominence of hilar vascular shadows. Electrocardiogram: normal. Liver aspiration biopsy: heavy hepatocellular and portal iron deposits. No increase in fibrous tissue, but aggregations of lymphocytes present in portal tracts.

Subsequent Progress: He continued in good health on a regime of fortnightly blood transfusions until September, 1951 when he developed a right sided lobar pneumonia and died within 24 hours in spite of vigorous therapy.

Summary of Post Mortem Findings: There were localised areas of brownish pigmentation on the anterior thorax, the shoulders and on the lower abdomen. There was moderate enlargement of the inguinal glands. Two pints

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of straw-coloured fluid were present in the right pleural sac and there was a collapse of the right lung with scattered areas of consolidation and an overlying pleurisy. The heart was normal. The liver was enlarged (weight: 2780 grams) and had a brownish colour. It gave a positive Prussian blue reaction. The spleen was moderately enlarged (weight: 1145 grams) and showed congestion. There was also enlargement of the mesenteric lymph glands.

Microscopically: The liver showed numerous foci of lymphocytic infiltration tending to occupy the periportal areas. Amongst these foci, liver cells could be identified as well as small bile ducts. The liver cells were normal and contained iron granules. The most heavily pigmented liver cells were those in lymphocytic foci and round the centrilobular veins. There was no evidence of increased fibrosis in the liver. The spleen showed a reduction in lymphatic tissue and Malpighian corpuscles were scanty. It was chiefly composed of a highly congested red pulp with extensive haemorrhagic areas. Scattered amon st the cells of the red and white pulp were occasional ma..ophages containing iron pigment. There was no evidence of iron in the jejunum which showed advanced autolysis. Mesenteric and para-

/aortic ...

aortic lymph glands showed a destruction of the normal architecture with no evidence of lympoid follicles or of medullary:cortical differentiation. Instead they were composed of a uniform mass of lymphocytes. The sinusoids under the capsule were congested, showing occasional haemorrhagic areas and numerous iron-filled macrophages. The kidneys contained numerous areas of lymphocytic infiltration, particularly in the subcapsular region. Otherwise they were normal and there were no iron deposits. The adrenals showed no abnormality except for small medullary foci of lymphocytic infiltration. There were a moderate number of iron-containing macrophages of the cortex. The testes showed marked involution with no evidence of spermatogenesis. The tubules were composed entirely of Sertoli cells on a thickened basement membrane. Occasional macrophages in the intertubular connective tissues were filled with iron-containing pigment. The prostate showed a number of foci of lymphocytic infiltration while the number of alveoli seemed to be reduced. There was no iron-containing pigment. The thyroid contained well filled colloid vesicles subtended by flattened epithelial cells i.e. resting phase. A number of cells had fine iron-containing granules in the supranuclear part of

/the ...

the cytoplasm. The lungs were markedly congested with evidence of bronchopneumonia. The pleura was thickened and showed areas of lymphocytic infiltration. It contained a number of macrophages pigmented with iron. The heart was normal; there was no evidence of iron present. The nerve cell layers of the cerebral cortex showed no abnormality. Occasional capillaries were filled with lymphocytes but there was no iron pigment.

CASE 12: a European male, aged 71 years, was first seen in September, 1950 when he had already received over 120 blood transfusions for a refractory anaemia. He was then in good health and his haemoglobin level was maintained by regular blood transfusions. His condition had been diagnosed 4 years previously when he began to complain of tiredness and found he was bruising easily. The only relevant findings at the time were a gross anaemia associated with purpura. Bone marrow aspiration revealed an aplasia involving all the blood elements.

He was treated with liver and iron but there was no response. Finally blood transfusions were commenced. However, he had to be readmitted to hospital several months later because of marked weakness. He was again

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found to be very anaemic (Haemoglobin 3.9 gram.%) and he was given a further 2,500 ccs. blood while in hospital. Since that time he had been well controlled by blood transfusions at intervals of 2-4 weeks. Further marrow aspirations had revealed no change in the aplasia of the bone marrow.

On Physical Examination: in September, 1950 (i.e. about 4 years after the commencement of the anaemia) there was marked dark brown pigmentation of the back of the neck, the lower parts of the forearms and the ankles. Clinically there were no signs of anaemia. The blood pressure was 160/95 mm.Hg. and there were no obvious abnormalities of the cardiovascular and respiratory systems. The liver was 5 fingers enlarged and was firm and non-tender. There was no splenomegaly or adenopathy. Hair distribution was normal and there was no abnormality of the gonads.

Laboratory Data: (After 124 pints of blood).
Blood count: Haemoglobin 14.8 grams%, erythrocytes per c.mm. 4,760,000, leucocytes per c.mm. 7,400, neutrophils 56%, monocytes 2%, lymphocytes 42%, eosinophils 0%, basophils 0%, reticulocytes 1%, Sedimentation rate (corrected): slight increase. Modified Ide test for Syphilis: negative. Urine analysis: nil chemically

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or microscopically; no excess of urobilin. Liver Function: Thymol turbidity 4.5 units, thymol flocculation one + positve. Takata-Ara reaction (Ucko's modification) one + positive. Icteric index 20 units. Prothrombin index 89%, Alkaline phosphatase 12.2 King Armstrong units. Blood proteins 3.9 grams %. albumin, 3.4 grams% globulin. Sugar tolerance (after 50 grams glucose orally): fasting level 100 mgm.%, ½ hour 120 mgm.% 1 hour 110 mgm.%, 1½ hours 125 mgm.%, 2 hours 100 mgm.% Blood and urinary diastase: normal. Fats in faeces: no excess. Electrocardiogram: standard leads showed left axis deviation. There was no evidence of any conduction defect and unipolar lead showed flattening of T waves over V_{4-6}. Liver aspiration biopsy; heavy deposits of iron in liver lobules and in the portal tracts. Moderate portal fibrosis with bile duct hyperplasia.

Subsequent Progress: Since September, 1950 the patient has continued in good health. Blood transfusions are only required 4-6 weekly now. A more recent bone marrow aspiration revealed a hypercellular marrow with a normoblastic response. There has been no evidence of haemolysis as judged by a reticulocytosis, or by increased urinary urobilin.

CASE 13: a European female aged 49 years was first

/studied ...

studied in September, 1950 when radioiron absorption was measured. At that time she had received 124 blood transfusions for aplastic anaemia. She had originally presented in 1947 with tiredness and breathlessness on exertion, when her red blood count was less than 1,000,000 cells per c.mm. A one marrow aspiration at that time showed a red cell aplasia and this finding was subsequently confirmed on repeated sternal punctures. After failing to respond to liver injections and iron she was started on a regime of repeated blood transfusions. These were given at 2-3 weekly intervals in the following three years so that by September, 1950 she had received 124 pints of blood. During 1950 she had observed that her skin was gradually becoming brown in colour.

On Physical Examination in September, 1950 there was a generalised slaty grey pigmentation of the skin. She was clinically mildly anaemic. The blood pressure was 100/70 mm.Hg. and both cardiovascular and respiratory systems appeared normal. The liver was enlarged 3 fingers below the costal margin, being firm, smooth and non-tender. There was no splenomegaly or lymphadenopathy and the hair distribution was normal.

Laboratory Data: (After more than 120 pints of blood)

/Blood ...

Blood count: Haemoglobin 10.0 grams %, erythrocytes per c.mm. 3,200,000. Leucocytes per c.mm. 2,800; neutrophils 46.5%, monocytes 1%, leucocytes 50.5%, eosinophils 1.5%, basophils 0.5%. Sedimentation rate: normal. Modified Ide test for Syphilis, negative. Urine analysis: nil microscopically or chemically except for slight excess of urobilin. Liver function: Thymol turbidity 1 unit, thymol flocculation, negative, Takata-Ara reaction (Ucko's modification) negative, Icteric index 9 units. Bilirubin under 0.5 mgm.%. Prothrombin index 100%. Blood proteins 2.7 grams% albumin, 3.2 grams % globulin. Sugar tolerance (after 50 grams glucose orally): fasting level 110 mgm.%, ½ hour 120 mgm.%, 1 hour 105 mgm.%, 1½ hours 95 mgm.%, 2 hours 85 mgm.%, Blood and urinary diastase: normal. Fats in stools: no excess. Electrocardiogram: normal. Liver aspiration biopsy: Heavy parenchymal and portal deposits of iron with early portal fibrosis.

Subsequent Progress: In the two years since the radioiron investigations were carried out the patient has continued to have blood transfusions every 2-4 weeks and her general health reamins fair.

D I S C U S S I O N

When the natural mucosal barrier to iron absorption is bypassed by the administration of repeated blood transfusions large quantities of iron may accumulate in the body. Thirtyone cases who have developed such a transfusional haemosiderosis have now been reported in the literature in some detail and to this group have been added the three cases described in the present study. The salient findings in all these subjects have been set out in Table IX. In addition Brown and co-workers[3] have recently reported the occurrence of a further 10 cases although full details are not given, and Bethell[1] has also made brief mention of another subject with aplastic anaemia who developed evidence of haemosiderosis after 138 transfusions. In all, therefore, 45 cases of the condition have now been reported and the majority of these have been recognised in the last 5 years. It is to be anticipated that there will be an ever increasing frequency of transfusional haemosiderosis with the easy availability and widespread use of intravenous blood in refractory anaemias. The only disease in Europeans in which comparable amounts of iron are to be found in the body is idiopathic haemochromatosis.

TABLE IX.

Author	Sex	Age	Diagnosis	Duration of Symptoms in Years.	Physical Findings: Diabetes	Hepato-megaly	Skin pigmentation	Marrow Findings	Number of Transfusions.	Iron in Transfusions (grams)	Iron in Liver (grams	Cause of Death	Post Mortem Findings.
Yates and Thalheimer (19 6)	M	65	Pernicious Anaemia	3					113			Anaemia	Liver not enlarged. Iron in marrow, ++ and Kupffer cells. ++ iron in parenchyma and stroma of pancreas.
Park (1937)	M	41	Aplastic Anaemia	11	++	+	+	Hypoplastic	290	31.5		?	Post mortem refused
Bomford and Rhoads (1941)	M	51	Refractory Anaemia	2½		-	+	Acellular	15			Broncho-Pneumonia	Liver: Haemosiderosis with early multilobular cirrhosis. Pancreas: Haemosiderosis with increased fibrous tissue. Excess in lymph glands.
	M	68	Refractory Anaemia	2		-	+	Hyper-cellular	12			Broncho-pneumonia with liver failure.	Liver: Haemosiderosis with multilobar fibrosis. Pancreas: Haemosiderosis with increased fibrous tissue.
	M	61	Refractory Anaemia	3	-		+	Partly mature cellular marrow	38+			Anaemia and broncho-pneumonia	Haemosiderosis and early fibrosis of liver and pancreas. Iron in lymph glands, heart and suprarenals.
Mawkey (19)	M	50	Aplastic Anaemia	"severe"	-	+		Cellular marrow	39.8 litres	20	28.8	Anaemia and broncho-pneumonia	Liver: ++ iron in parenchymal cells. Periportal fibrosis. + Iron in spleen, lymph nodes, pancreas and heart.
Humphreys and Southworth (1)	F	48	Thymoma with anaemia	3				Mild hypo-plasia	30			Congestive cardiac failure	Deposits of iron in liver, pancreas, bone marrow, thyroid adrenals, spleen and lymph nodes.
Zeltmacher and Bevans (1945)	M	85	"Aplastic" Anaemia	1	+	+	+	Cellular	17	6.5	29	Convective cardiac failure	Liver: ++ Iron in parenchyma and portal tracts with portal fibrosis. Pancreas: ++ Iron with increased fibrous tissue. Excess iron also in heart (fibrotic) thyroid, adrenals, prostate, lymph glands and kidney.
Ch ner (19 6)	M	14	Refractory Anaemia	6	-	-	+	Erythroid hyperplasia	6 litres	2.75	47	Mesenteric Thrombosis	Liver: ++ Iron in parenchyma and portal tracts. Pancreas: Haemosiderosis. Heart: Parenchymatous degeneration with increased iron.
Scow d lumer 9+8	F	19	Pyelonephritis with Anaemia	4	-			Relatively acellular	21			Uraemic coma.	Haemosiderosis of lungs, lymph nodes. Liver showed periportal fibrosis. Chronic glomerular nephritis.
	F	73	Aplastic Anaemia	2	-			Hypocellular	21			Pyelonephritis with pneumonia	Haemochromatosis of liver. Increased iron in spleen and pancreas.

TABLE IX (Continued)

Author	Sex	Age	Diagnosis	Duration of Symptoms in Years.	Physical Findings. Icterus	Hepato-splenomegaly	Skin Pigmentation	Marrow Findings.	Number of Transfusions.	Iron in Transfusions (grams).	Iron in Liver (grams	Cause of Death	Post Mortem Findings.
Schwartz and Blumenthalt (1948)	F	37	Aplastic Anaemia	¼				Replaced by fibrous tissue	75			Spreading thrombophlebitis.	No post mortem. Liver biopsy: Haemosiderosis with increased fibrosis of peri-portal tissues.
	F	47	Refractory Anaemia	4½	-	+	+	Hypercellular	75			Postoperatively after splenectomy.	Liver: Haemosiderosis with cirrhosis. Increased iron in pancreas, abdominal lymph glands and spleen.
	F	49	Refractory Anaemia	2	+	+	+	Hypercellular	58			Postoperatively after splenectomy.	Haemosiderosis of liver, stomach, adrenals, lymph nodes and pancreas. Pigment cirrhosis.
Muirhead et al (1949)	F	37	Haemolytic Anaemia	2/3	-	+		Erythroid hyperplasia	99	24.75	21.8	Subarachnoid haemorrhage.	Liver: ++ Iron in parenchyma and portal tracts. Increased iron in pancreas, lymph nodes, kidneys and heart.
	M	38	Haemolytic Anaemia	2	-				58	14.5	17.55	Hepatic failure.	Liver: Generalised iron deposition with portal fibrosis. + Iron in adrenals and kidneys.
	F	42	Refractory Anaemia	4	-				114	28.5	9.7	Subarachnoid haemorrhage	Liver: Increased iron in parenchyma and Kupffer cells. Early portal fibrosis. Pancreas: Slight fibrosis with ++ iron in parenchyma. Excess iron in all kidney tubules.
	F	39	Refractory Anaemia	2½	-			Acellular	16	4	3.7	Torulosis with pyelonephritis	Chronic hepatitis with excess iron in parenchyma and portal tracts. Portal fibrosis.
	M	63	Refractory Anaemia	13½	+				12	3	2.75	Hepatic insufficiency	Laennec's cirrhosis with ++ iron in parenchyma and portal tracts. Iron excess also in pancreas, heart, lymph nods. and kidneys, (proximal tubules).
Wyatt and Goldenberg (1949)	M	70	Myelofibrosis with Anaemia	1½	-	-		Myelofibrosis and sclerosis	38	8.2	4.4	Anaemia	Liver: ++ Iron in Kupffer cells, slight in parenchyma. Massive iron in spleen. Iron also present in lymph nodes and renal pelves.
	F	62	Refractory Anaemia	1¾	-	+		Cellular	35	7.6	12.5	Anaemia	Liver showed ++ iron in parenchyma nil in Kupffer cells. Spleen large with iron in macrophages.
	M	66	Myelofibrosis with Anaemia	2	-			Myelofibrosis	32	8	4.05	Leukaemia.	Bone marrow showed myelogenous leukaemia. Liver ++ Iron in Kupffer cells, slight in parenchyma.
	M	49	Myelosclerosis with anaemia.	2	-			Myelosclerosis	67	17			Still alive. Liver biopsy: Pronounced siderosis and early portal cirrhosis.

TABLE IX (Continued)

Author	Sex	Age	Diagnosis	Duration of Symptoms in Years.	Physical Findings. Oedema	Hepato-splenomegaly.	Skin pigmentation	Marrow Findings	Number of Transfusions.	Iron in Transfusions (grams)	Iron in Liver (grams)	Cause of Death	Post Mortem Findings.
Wyatt et al (1950)	M	67	Multiple Myeloma	2		+	-	Multiple Myeloma	29	6.8	4.6	Myelomatosis with broncho-pneumonia.	Liver: Siderosis mainly of Kupffer cells with early peri-portal fibrosis. No iron in kidney, pancreas or skin.
	F	75	Refractory Anaemia	3		-			9	2.2	2.6	? Nutritional deficiency.	Marked siderosis of liver and spleen.
	M	62	Refractory Anaemia.	2	-	+			135	33.7	75.7	Liver failure.	Cirrhosis of liver, with siderosis mostly of parenchyma. Heavy iron deposits in spleen, pancreas, adrenals, lymph nodes, myocardium, kidneys and bone marrow.
Womack and Brownlee (1950)	M	28	Refractory Anaemia	3½	-	+		Erythroid hyper-plasia.	136	33.6	26.7	Congestive cardiac failure.	Liver: Some central lobular necrosis with increased iron in hepatic ducts and Kupffer cells. Increased iron in pancreas. Heart hypertrophied with increased iron.
	F	5½	Refractory Anaemia	5	-		+	Hyper-plastic	360 litres				Still alive. Skin biopsy: ++ iron.
Norris and McEwan (1950)	F	71	Aplastic Anaemia	5	+		+	Hypo-plastic	± 100			Gastrointestinal haemorrhage	Siderosis of skin, ovaries, adrenals, spleen, kidney, heart, thyroid. ++ Iron in liver. No cirrhosis.
Van Rijssel and Kroese (1951)	M	23	Refractory Anaemia	4	-	+	+	Cellular marrow	25 litres	12.5	10	Septicaemia.	Cirrhosis of liver with ++ iron in parenchyma and in Kupffer cells. Excess iron in pancreas with increased fibrous tissue. Iron also + in skin, adrenals, stomach, heart, spleen (removed at operation) pituitary and in distal kidney tubules.
Clinico-Path. Conference at PostGraduate Medical School. (1952).	F	22	Refractory Anaemia	6+	-	+	+	Cellular marrow later aplastic	210	40		Multiple haemorrhages and lung abscesses.	Infantilism. Siderosis of liver with some portal fibrosis. Spleen (removed 6 years before death) normal. Siderosis of pancreas and lymph nodes.
Authors' Cases	M	44	Chronic lymphatic leukaemia with refractory anaemia.	5	-	+	+		150+			Broncho-pneumonia.	Numerous foci of lymphocytic infiltration in portal areas of liver. Heavy iron deposits in parenchyma and in portal tracts. Lesser iron deposits also present in spleen, abdominal lymph glands, adrenals, testes and thyroid. (No sections of pancreas available).
	M	71	Aplastic Anaemia	5	-	+	+	Acellular marrow.	120			-	Still alive. Liver biopsy: Increased iron in parenchyma and portal tracts. Moderate portal cirrhosis.
	F	49	Refractory Anaemia	3	-	+	+	Acellular marrow initially. Later hyper-plastic	124				Still alive. Liver biopsy: Increased iron in parenchyma and portal tracts. Some portal fibrosis with bile duct hyper-plasia.

CLINICAL FINDINGS:

The conditions for which repeated blood transfusions were given varied in the 34 cases of transfusional haemosiderosis listed in Table IX. These were a variety of refractory anaemias including those with cellular and acellular marrows, haemolytic anaemias, myelofibrosis, chronic leukemia, multiple myeloma and pernicious anaemia before the advent of liver therapy. The number of transfusions given varied from 6 to 390. There was a range of age from 5 years to 73 years (mean 48 years) while the male-female ratio was approximately 3:2 (20 males and 14 females). Diabetes was present in only 5 of the subjects. In one its presence seemed to be incidental (16), in another it was demonstrated by a raised blood sugar only (13), and in two others it was so mild as not to require any treatment (20),(27). Hepatomegaly was commented on in about half the cases as was some degree of skin pigmentation. The mode of death could usually be related to the underlying condition for which transfusions were being given, the most frequent cause being terminal broncho-pneumonia superimposed on anaemia. Liver failure was mentioned in only three cases. Congestive cardiac failure was also terminally

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present in another three but Brown et al [3] found "manifestations of cardiac failure" in six of the nine adults observed by them. These subjects, however, had shown moderate to severe degrees of anaemia for years and were often in an age group where coronary artery disease is common.

On the clinical evidence there would therefore seem to be little reason to incriminate the excessive iron deposits in transfusional haemosiderosis as harmful to the body. The hepatic and pancreatic insufficiencies so characteristic of idiopathic haemochromatosis were infrequent. In addition signs of endocrine hypofunction were rare while myocardial failure, when present, could be ascribed usually to other causes.

PATHOLOGICAL FINDINGS

The most constant findings at postmortem were a heavy increase in the iron content of the liver and spleen, with variable amounts present in other organs including the pancreas, kidneys, heart, adrenals, lymph glands and bone marrow. The distribution of iron in the liver was both parenchymal and in the portal tracts with a tendency to heavier deposits in the latter site. However, this was by no means constant. In 21 of the

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cases there was evidence of portal fibrosis but this was usually of a mild degree. There were thus definite similarities between the postmortem findings in transfusional haemosiderosis and those present in idiopathic haemochromatosis. In view of certain experimental evidence this is not surprising. Dubach and co-workers (9) have shown that only 1.5% of the iron liberated from the breakdown of donor blood is reutilised for haemoglobin synthesis in refractory anaemias. The major portion of the remaining liberated iron is then taken up initially by the reticulo-endothelial system and is deposited especially in the spleen, lymph nodes, bone marrow and in the Kupffer cells of the liver. However, as the quantity of iron in the body increases, redistribution of the iron occurs and there is an overflow of iron into parenchymal tissues throughout the body (9). It is therefore not surprising that there are resemblances between the pathological findings in the later stages of transfusional haemosiderosis and those in idiopathic haemochromatosis. However, differences are definitely present. In transfusional haemosiderosis there are usually heavy depositions of iron in the spleen and bone marrow while deposits in the heart are scanty or absent; haemofuscin is not found and pancreatic fibrosis is an uncommon feature. Kidney deposits, as in idiopathic haemochromatosis, tend to be minimal (21).

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The importance of excessive iron, however, does not depend primarily on its distribution. More important is its possible capacity to produce damage in the organs in which it is deposited. The bulk of the iron was present in the liver of the 34 cases of transfusional haemosiderosis analysed in Table IX. Some degree of portal fibrosis was found in 21 of these cases but there seemed to be no correlation between the number of transfusions given and the development of fibrosis. In the 21 cases who showed this finding an average of 60 transfusions (range 12-210) had been given, while the remaining 11 cases who showed no evidence of portal fibrosis had received an average of 68 (range 10-150). Animal experimental evidence also seems to lend some support to the thesis that iron itself does not produce cirrhosis of the liver. Rous and Oliver (19) injected rabbits' blood into rabbits for several months without producing cirrhosis and similar results were obtained by Polson (13) with dialysed iron intravenously. More recently Brown and co-workers (3) injected up to 9 grams of saccharated iron oxide into dogs over periods of 44-68 days. The animals were then followed for periods up to 15 months. Sugar tolerance remained normal and there was no evidence of electrocardiographic abnormality. Biopsies six months after injections were begun showed a siderosis of the liver,

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spleen, pancreas, lymph nodes and skin. In the liver most of the iron was present in the portal tracts and there was no fibrosis. In all these animal experiments, however, there is a relatively brief follow-up.

The only other available evidence about the possible long-term toxic effects of iron is in idiopathic haemochromatosis. It has recently been shown (7) that pronounced subjective improvement with diminution in liver size, improvement in liver function and in carbohydrate metabolism occur in this condition with the mobilisation of excessive iron by repeated phlebotomies. On this evidence it is difficult not to incriminate the heavy iron deposits in the liver for at least some part in the development of portal fibrosis in transfusional haemochromatosis. Other factors, such as the anoxia accompanying the anaemia itself may be important although there is no evidence that anaemia alone causes cirrhosis. It is also possible that agents which damage bone marrow enough to lead to refractory anaemia may also have hepatotoxic effects. Another suggestion is that individuals with refractory anaemias now live long enough on donor blood for certain cellular decadent alterations to reveal themselves in organs with a high metabolic activity (25). However, this is speculation and all

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that can be noted with certainty is that a high percentage of patients who have refractory anaemia treated over long period with blood transfusions develop portal fibrosis, but that this is not usually of sufficient extent to interfere with liver function.

THE METABOLIC DEFECT.

Superficially there would seem to be no connection between the underlying metabolic defect in idiopathic haemochromatosis and in transfusional haemosiderosis. In one the excessive iron deposits are derived from increased intestinal absorption, whereas iron introduced via blood transfusions is the source of the other. However, that there is some relationship between the two conditions is suggested by the fact that several cases of transfusional haemosiderosis have shown greater quantities of iron in the liver alone at autopsy than was contained in all the blood transfusions administered. (See Table IX). In the majority of these cases the discrepancy between the amount of iron in the transfusions and the quantity in the liver was not large. In three, however, the difference between the amount of iron in donor blood and the quantity found in the liver at autopsy was very large. In has therefore

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been suggested that some continuation of intestinal iron absorption and storage (25) may occur in transfusional haemosiderosis. Although attractive, this explanation does not seem to be the only possible one for the phenomenon of abnormally high iron stores in some cases. Accurate estimation of iron in tissues is hindered by the difficulty of eliminating all the blood from them. Results, therefore, tend to be too high. However, there is evidence that this error is a small one and it should not affect the results significantly (6). It is also possible that higher figures than predicted may be obtained if the basic mechanism of the anaemia for which blood transfusions are given is a haemolytic one. Evidence of haemolysis was, however, lacking in most of the cases who showed more iron in the liver than could be accounted for by the transfusions. A feature common to the few cases of this type in whom bone marrow aspirations had been carried out was the uniform finding of a hypercellular marrow. It is therefore possible that they represented examples of the "erythronoclastic response" reported recently by Huff and co-workers (12). These writers found in a series of intravenous radioiron turnover studies on refractory anaemias that iron may go to the marrow in a normal fashion but that on leaving the

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marrow as haemoglobin only a small portion may appear in the peripheral blood while the major portion accumulates in the spleen. One such patient exhibited a hyperplastic marrow with a refractory anaemia, but without evidence of haemolysis, the reticulocytes being low, the Coombs antiglobulin test negative, and the faecal urobilinogen content normal. It thus seems possible to have continuous blood breakdown taking place with the subsequent release of iron and no evidence of haemolysis.

Two possible explanations are therefore available to account for the presence of higher than anticipated iron stores in some cases of transfusional haemosiderosis. They may be the result of continuation of intestinal iron absorption or may be due to the fact that the anaemia requiring transfusions is of an unusual haemolytic type. It was to investigate these two possibilities that radioiron absorption and utilisation studies were carried out in the three subjects described in the present investigation.

The radioiron studies in these three cases support to some extent both iron absorption from the bowel and an unusual type of haemolytic reactions as factors accounting for the discrepancies between the amount of iron administered in transfusions and that present in the liver. In two

of them (cases 11 and 13) the utilisation of absorbed iron was very low but faecal analyses and in vivo counts in two separate studies on one of these (case 13) suggested that iron absorption was not completely absent, although it was less than normal. In the third case (case 12) a significant blood uptake of 3.5% of the administered dose was recorded. The unusual feature of this case was the short period that this level was maintained in the blood as it dropped to 0.7% between the 15th and 30th days after the adminstration of the iron. As the normal life span of mature red cells is about 90-120 days [4], it seemed that this patient's blood was being broken down in an abnormal fashion although no evidence of haemolysis was present. He had previously been aplastic on marrow aspirations but sternal puncture subsequent to the radioiron studies revealed a hyperplastic normoblastic marrow.

It, therefore, seems that iron absorption may continue to occur from the gut in spite of saturated iron stores but that such a finding is more likely to occur in cases with hypercellular marrows and an associated haemolysis. This case also showed that the iron being absorbed from the gut was being utilised for haemoglobin synthesis in preference to the enormous

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stores already present in the body. This would seem to confirm Dubach and co-workers' observation that the most recently absorbed iron is the most easily available for haemoglobin synthesis [9]. On the results of these radioiron investigations it seems that the discrepancy between the amount of iron in the liver at autopsy and the amount given in donor blood may therefore rest on two factors, viz. the nature of the original anaemia and a continuation of some degree of iron absorption even in the face of widespread transfusional haemosiderosis. In none of the three cases investigated was a pattern of iron absorption and utilisation found which resembled that in idiopathic haemochromatosis.

The degree of intestinal absorption shown to be present by these radioiron studies can account for the minor differences found between the quantity of iron in the liver at autopsy and the quantity present in administered blood in several of the cases of transfusional haemosiderosis described in the literature. However, in three reported cases the discrepancy was so great that they seem worthy of more detailed analysis. The one subject reported by Zeltmacher and Bevans [27] was a 65 year old male who presented initially with congestive cardiac failure and a refractory anaemia with a hyper cellular marrow. He was also found to have some skin

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pigmentation, hepatomegaly and decreased sugar tolerance. He received only 12.8 litres of blood, the major portion of this being in the last few weeks of life. At autopsy he showed the classical features of idiopathic haemochromatosis and had 29 grams of iron in the liver although he had only received 6.5 grams in transfused blood. The second case reported by Chesner (5) was a boy of 14 with a six year history of anaemia who showed hyperplasia of the erythroid elements on marrow aspiration. There was no skin pigmentation, sugar tolerance was normal and there was no obvious endocrine hypofunction. In all, he received 6 litres of blood containing 2.75 grams of iron. He died from a portal and mesenteric vein thrombosis and showed the typical features of idiopathic haemochromatosis at autopsy with 47 grams of iron in the liver. The third subject reported by Wyatt and co-workers (25) is more difficult to evaluate because of insufficient clinical data. However, at autopsy he presented "a morphologic duplication of idiopathic haemochromatosis". He had received 33.7 grams of iron in blood transfusions and showed 75.7 grams in the liver at autopsy. There is therefore some evidence to suggest that these three cases represented examples of true idiopathic haemochromatosis, who subsequently developed refractory anaemias. The absence

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of clinical signs in the second case may be ascribed to the fact that he died from an intercurrent condition at an age before the usual manifestations of the disease become apparent. Some support for the contention that these cases were each suffering from idiopathic haemochromatosis is given by the recent description (11) of a classical case with skin pigmentation, diabetes, evidence of endocrine dysfunction and a typical liver biopsy who had an associated refractory anaemia with a hypercellular marrow. This subject had received no blood transfusions. Sheldon (21) found only 6 cases of idiopathic haemochromatosis with blood counts below 2,500,000 but recently Koszewski (14) found 9 cases of megaloblastic anaemia in a series of 35 patients with idiopathic haemochromatosis investigated. It, therefore, seems that the association of two such rare conditions as idiopathic haemochromatosis and refractory anaemia may be due to more than chance in these reported cases. It is probable that the haemochromatosis occurred initially in these subjects as it takes many years for the enormous iron stores to accumulate. The subsequent development of a refractory anaemia in such cases may possibly be related to the inability of an iron laden cirrhotic liver to deal with potential marrow toxins.

SUMMARY AND CONCLUSIONS

(1) Three additional cases of transfusional haemosiderosis are described and the literature on the subject is reviewed.

(2) The clinical and pathological features present in transfusional haemosiderosis are analysed and the similarities and differences between them and those found in idiopathic haemochromatosis discussed.

(3) In several cases of transfusional haemosiderosis reported in the literature more iron was found in the liver alone at autopsy than was contained in all the blood transfusions administered. Radioiron investigations on the subjects presented in this study showed that this extra iron may be derived from a continuation of absorption of iron from the bowel. Evidence is also produced to suggest that an abnormal type of haemolytic reaction may account for some of the iron stores in a proportion of cases of transfusional haemosiderosis.

(4) Three cases reported in the literature showed an enormous discrepancy between the quantity of iron in the liver at autopsy and that administered in donor blood. It is suggested that these cases represented true examples of idiopathic haemochromatosis who subsequently developed refractory anaemias.

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C H A P T E R V.

FINAL SUMMARY AND CONCLUSIONS

The present investigation was started in order to compare the pattern of iron absorption and utilisation in three conditions where excessive deposits or iron are found in the body, viz. idiopathic haemochromatosis, malnutritional cytosiderosis, and transfusional haemosiderosis. For this purpose 6 cases of idiopathic haemochromatosis, 5 cases of malnutritional cytosiderosis, and 3 cases of transfusional haemosiderosis were studied using radioiron and the results obtained in each group were compared with each other and with those in 9 control subjects. In addition, full clinical, laboratory and pathological data were gathered on each case studied in order to compare the presentation and metabolic defects in each group and their possible relationship to each other.

Radioiron studies in idiopathic haemochromatosis showed an increased absorption of iron from the gut as compared with a group of control subjects. A proportion of the absorbed iron was utilised for haemoglobin formation and the remainder was deposited in the liver and other organs. Two young cases with the disease showed a strikingly high absorption and it is probable that this finding accounts for the poor prognosis in

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younger subjects. The clinical and pathological findings were discussed with special reference to the cardiac complications. It is suggested that the frequent occurrence of myocardial failure in young cases with idiopathic haemochromatosis is due to the rapid deposition of iron in cardiac muscle which occurs secondary to a high intestinal absorption. Finally the possible therapeutic value of repeated phlebotomies in idiopathic haemochromatosis was discussed.

Iron absorption seemed to be very low in 4 cases of malnutritional cytosiderosis studied while in hospital. A higher absorption was recorded in a fifth subject who was investigated on his natural diet. It is probable that the condition occurs secondary to the ingestion of large quantities of iron in the Bantu diet and that, unlike idiopathic haemochromatosis, it affects primarily the reticulo-endothelial system. However, the possibility that there is, in addition, some mucosal defect present which allows for a relatively greater degree of iron absorption, has not been excluded. The clinical presentation of at least 3 of the cases investigated was very similar to that in idiopathic haemochromatosis although this has not been the experience of other workers. However, there were definite differences

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in the pathological findings as heaviest iron deposits tended to be present in the reticulo-endothelial system rath r than in glandular tissues.

Iron absorption was low in 2 of the 3 cases of transfusional haemosiderosis investigated. 'owever, it did not seem to be completely absent in these cases while in a third one a significant blood level of radioiron was recorded. There was, therefore, definite evidence to suggest that iron absorption may continue to occur in spite of saturated body stores. A possible explanation is therefore available to account for the fact that several cases of transfusional haemosiderosis have been described in which more iron was present in the liver alone at autopsy than had been contained in all the administered blood. The radio-iron studies in one case also suggested that an abnormal for- of haemolysis may account for a proportion of the iron stores in transfusional haemosiderosis The clinical and pathological find ngs in transfusional haemosiderosis were presented and the literature on the subject reviewed. There w s little clinical evidence that the iron deposits proved harmful to the body in transfusional haemosiderosis and the pathological presentation showed definite differences from that in idiopathic haemochromatosis. However, evidence was

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produced to suggest that three cases of transfusional haemosiderosis reported in the literature were, in fact, true cases of idiopathic haemochromatosis who subsequently developed refractory anaemias requiring repeated blood transfusions.