A CASE OF PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA ASSOCIATED WITH SECONDARY HAEMOCHROMATOSIS, A LOWER NEPHRON NEPHROSIS, AND A MEGALOBLASTIC ANAEMIA

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Secondary or exogenous haemochromatosis has been defined by Auferheide, Horns, and Goldish (1953) as a condition acquired as “a consequence of anaemia, blood transfusion, or both, and characterized by increased hepatic and total body iron and unequivocal portal cirrhosis.” These authors found only 20 cases in the literature and have added two more of their own. They comment on the lack of adequate evidence of true portal cirrhosis in many of the cases described.

The association of paroxysmal nocturnal haemoglobinuria (P.N.H.) and secondary haemochromatosis has not been previously described. Each of these conditions produces characteristic but totally dissimilar patterns of iron distribution in the body. In classical paroxysmal nocturnal haemoglobinuria renal haemosiderosis is associated with depletion of the normal iron depots, while in secondary, as in primary, haemochromatosis the body tissues are saturated with iron but the kidney contains little or none. The iron distribution in these two conditions represents the results of opposing processes. In paroxysmal nocturnal haemoglobinuria there is a constant daily loss of iron, whereas in secondary haemochromatosis iron is accumulated in the body tissues.

In this paper we propose to discuss the pathogenesis of this unusual and paradoxical combination of iron distribution.

The occurrence of a fatal lower nephron nephrosis and the presence of a megaloblastic anaemia lend further interest to the case.

Clinical Data

The patient, a housewife aged 44 years, was first seen in June, 1949. She was admitted to hospital with the signs and symptoms of a severe anaemia. There was an associated history of menorrhagia and bleeding haemorrhoids. The skin had a faint icteric tinge and the liver edge was easily palpable. The initial blood count was: Hb, 1.7 g. per 100 ml.; red cells, 545,000 per c.mm.; colour index, 1.1; white cells, 4,000 per c.mm.; and platelets, 51,000 per c.mm. The red cell fragility test was normal. Sternal puncture showed a normoblastic hyperplasia. The Wassermann reaction was negative. The serum bilirubin level was 0.8 mg. per 100 ml. and the remaining liver function tests were normal. Following transfusion with 2 pints of blood, and the administration of “ferrivinen” and oral iron, the haemoglobin rose to 10 g. per 100 ml., and the patient was discharged with instructions to continue oral iron at home.

In September, 1950, she was readmitted with a recurrence of the symptoms of anaemia and an exacerbation of the menorrhagia. The Hb was now 4.5 g. per 100 ml. The liver was still enlarged and a second sternal marrow puncture showed that erythropoiesis was again normoblastic. Two pints of blood were given, and a tinge of jaundice present on admission became more obvious. The serum bilirubin level was 2.5 mg. per 100 ml., the serum alkaline phosphatase 22 King–Armstrong units per 100 ml., thymol turbidity 14 units, thymol flocculation 4+, and serum colloidal gold 5. Treatment with “ferrivinen” and oral iron restored the haemoglobin to 10 g. per 100 ml. A hysterectomy was then performed. Shortly afterwards she was sent home and instructed to continue taking oral iron.

In August, 1952, she was again readmitted with Hb 3.5 g. per 100 ml., colour index 1.1, and a reticulocyte count of 8%. The liver was still enlarged and the marrow again showed normoblastic erythropoiesis. Marked generalized brown skin pigmentation was noted for the first time. The liver function tests were as before and the serum proteins were normal. After treatment with a pint of packed cells followed by a course of oral iron she was discharged in September, 1952.

In January, 1953, she was readmitted for the fourth time with a recurrence of symptoms. The brown pigmentation of the skin had increased. The liver was still palpable. The Hb was 4.5 g. per 100 ml. and the
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colour index 1.3. A sternal marrow puncture now showed megaloblastic erythropoiesis. A review of the previous marrow smears confirmed the absence of megalopoiesis in them. The stomach contained free acid and a four-day fat balance showed a 93% fat absorption. A diagnosis of megaloblastic anaemia associated with cirrhosis of the liver was entertained at this stage. Despite a course of intramuscular vitamin B12 and a crude liver extract, the marrow remained predominantly megaloblastic. A course of folic acid, however, produced a reticulocyte response of 36% and erythropoiesis was now normoblastic. A glucose tolerance test was normal.

Haemoglobinuria was first noted during this period of admission. When questioned, the patient admitted having passed dark urine on many occasions during the previous three or four years. Oxyhaemoglobin was detected spectroscopically in the urine and was present in the absence of whole red blood cells. Haemoglobinuria was also noted. The direct and indirect Coombs tests were negative. No cold agglutinins or cold or warm haemolysins could be demonstrated. There was no increase in the red cell osmotic fragility. The Ham test (Ham, 1939) and Crosby’s modification of this test (Crosby, 1950) were positive. The Heglin and Maier (Heglin and Maier, 1944) and Schum’s tests were positive. On the basis of these findings, a diagnosis of paroxysmal nocturnal haemoglobinuria was made. The patient was discharged in May, 1953.

In February, 1954, the patient was admitted for the last time. She had been having attacks of vomiting attributed by herself to the taking of iron tablets. The Hb was 4.5 g. per 100 ml. and the colour index was 1.2. Anticoagulant therapy was begun and the prothrombin level maintained between 15 and 25% of average normal for a fortnight. No apparent improvement followed, and it was decided to transfuse packed cells which had been washed three times. A severe reaction followed. The patient complained of severe abdominal pain and vomited two to three hours after transfusion. Laboratory tests, including the Coombs test, showed no incompatibility. Jaundice and oliguria followed, the blood urea rose rapidly to 320 mg. per 100 ml., anuria developed, and despite prompt institution of the Bull régime the patient died 10 days after transfusion.

Post-mortem Findings

A complete necropsy was performed five hours after death. The body was that of a fairly well nourished middle-aged woman, with diffuse bronze pigmentation of the entire skin. Many small, unpigmented acne scars were present on the face. A lower abdominal operation scar was noted. There was no caput medusae.

The heart was of average size and weighed 300 g. There was no apparent valvular or coronary artery disease. The myocardium was browner than normal. The left pleural cavity contained a small effusion. The left lung weighed 220 g. and the right 300 g. They were grossly normal. The liver weighed 1,800 g. and its lower border projected 4 cm. below the costal margin. Its surface showed a coarse irregular nodulation. The cut surface was a dark bronze. The gall bladder and biliary ducts showed no anomaly. The pancreas was a pale yellowish-brown. Grossly it appeared normal. The spleen weighed 200 g. Its cut surface was bronzed. Many of the abdominal lymph glands were enlarged and were of a rusty brown. The adrenals showed irregular brown pigmentation of the periphery of their cortices.

The kidneys were about equal in size; the right weighed 120 g. and the left 110 g. Their capsules were thickened and when stripped left a granular surface. The cortices were regular but somewhat narrowed and showed deep bronze pigmentation, while the pyramids were a brownish-grey. The hilar fat was increased.

The cerebral vessels and meninges were normal. A few small petechial haemorrhages were present in the pons, otherwise the brain was normal.

Red bone marrow hyperplasia was indicated by the presence of red marrow occupying the entire shaft of the femur.

Chemical analysis of the liver showed a total iron content of 21 g.

Microscopic Findings

The skin showed marked brown pigmentation of the basal cells of the Malphigian layer. The pigment gave a negative Prussian-blue reaction, was bleached by hydrogen peroxide, and Fontana’s stain for melanin was positive.

The liver exhibited a marked increase in the perportal connective tissue with intercommunicating portal areas and distortion of the hepatic architecture; considerable bile-duct proliferation was present in the portal areas. The appearances were those of a portal cirrhosis. In addition there was a massive hepatic haemosiderosis with heavy deposits of haemosiderin in the liver cells, Kupffer cells, and portal connective tissue. The bile canaliculi contained only minute traces of stainable iron.

The pancreatic acini contained moderate scattered deposits of haemosiderin. The islets were little affected. Occasional foci of fibrosis were noted.

The spleen and lymph glands contained considerable haemosiderin deposits, these being concentrated mainly in the histiocytes and littoral cells of the dilated sinuses.
Fig. 1.—Liver showing well-marked portal cirrhosis and haemosiderosis.

Fig. 2.—Kidney with heavy deposition of haemosiderin in the cells of the convoluted tubules.

Fig. 3.—Kidney cortex, in which two fibrosed and three normal glomeruli are shown.

Fig. 4.—Renal medulla with many collecting tubules filled with haemoglobin casts.
The salivary glands contained small traces of haemosiderin. None was detected in the sweat glands.

The stomach mucosa appeared healthy and most of the glands contained haemosiderin.

The myocardial fibres contained small deposits of haemosiderin, situated at each pole of their nuclei in the position of the lipochrome of brown atrophy. Some fibres showed the presence of lipochrome without associated haemosiderin.

The muscle fibres of the tongue contained small traces of haemosiderin.

All smooth muscle appeared free of haemosiderin.

The lungs were emphysematous and showed minute scattered traces of haemosiderin, situated in phagocytes in the alveolar wall and free in the alveoli.

The pituitary contained small scattered deposits of haemosiderin, but there was no evidence of associated parenchymatous damage.

The thyroid was free of pigment.

The adrenal cortex contained considerable deposits of haemosiderin concentrated almost entirely in the glomerular zone.

The kidney’s capsule was thickened and its cortex somewhat thinned. Large amounts of haemosiderin were present in the epithelial cells of the cortical tubules. Many tubules contained large fragments of haemosiderin lying free within their lumen. Some were dilated and showed degenerative and desquamative changes. Occasional small groups of subcortical tubules were atrophied and consisted of contracted tubules lined by a flattened epithelium with haemosiderin filling their small lumen. These groups were obviously not functioning and showed related chronic inflammatory cells. The glomeruli and arterioles contained no haemosiderin. A considerable number of fibroed glomeruli were scattered throughout the cortex and there was a general increase of fine interstitial fibrous tissue. Most of the collecting tubules were distended by haemoglobin casts. Degenerative tubular cells were adherent to the casts, which were being attacked by polymorphs and macrophages. Foreign-body giant cells were seen in relation to some. Signs of regeneration were present in some tubules. These were lined and partly filled by a newly proliferated cubical epithelium. Scattered chronic inflammatory cells were present in the somewhat oedematous interstitial tissue of the medulla.

The final diagnosis included paroxysmal nocturnal haemoglobinuria, lower nephron nephrosis, and secondary haemochromatosis.

Discussion

Renal Damage and Paroxysmal Nocturnal Haemoglobinuria.—Crosby (1953) points out that the intense renal siderosis so characteristic of paroxysmal nocturnal haemoglobinuria does not, apparently, lead to impairment of renal function. When renal failure does occur it is generally a sequel of recurrent attacks of pyelonephritis. On the other hand, Heitzman, Campbell, and Stefanini (1953) described the development of a “haemosiderin nephrosis” in a case of paroxysmal nocturnal haemoglobinuria. During the course of their patient’s illness a lower nephron nephrosis with anuria developed following transfusion with heparinized blood. Recovery followed after 14 days and the patient died nearly three years later from extrarenal causes. They discuss the relative parts played by the haemosiderosis and the lower nephron nephrosis in the production of the tubular degeneration and interstitial fibrosis which were such prominent features in their patient’s kidneys. They concluded that the intense renal siderosis was responsible for the greater part of the renal damage and that the lower nephron nephrosis which had occurred three years previously contributed only slightly to the final renal pathology.

In our case there is also evidence of renal damage produced by haemosiderin deposition, although not to the same extent found by Heitzman. The fibroed glomeruli, the contracted and atrophied tubules filled with haemosiderin, and the fine interstitial fibrosis can reasonably be attributed to the long-standing accumulation of haemosiderin, and not to the lower nephron nephrosis, which was only of 10 days’ duration. Nissim (1953), by administering large doses of parenteral saccharated iron oxide to animals, has produced renal damage consisting of cloudy swelling and nuclear degeneration of the cells of the proximal convoluted tubules. Some cellular infiltration was also present around the degenerated tubules and intertubular foci of iron-laden phagocytes was also noted. It would thus appear that severe renal siderosis may produce a varying degree of kidney damage.

Anuria in Paroxysmal Nocturnal Haemoglobinuria.—The development of a fatal lower nephron nephrosis appears to be extremely uncommon. Crosby (1953) lists the causes of death in 53 cases, and lower nephron nephrosis is not mentioned amongst them. The rarity of a fatal lower nephron nephrosis is rather surprising, since almost all these patients receive numerous transfusions which are frequently followed by haemolytic crises.
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of varying severity. Haemolysis here is due to the presence in normal, fresh plasma of a heat-labile haemolytic factor to which the cells of patients with paroxysmal nocturnal haemoglobinuria are unduly sensitive, thus causing haemolysis of the patient's own cells and not those of the donor (Dameshek and Neber, 1950). The heat-labile factor responsible for this "plasma transfusion reaction" deteriorates on storage. If the red cells are freed from plasma by adequate washing with saline the reaction will not occur. Patients vary greatly in their sensitivity to this heat-labile factor. Crosby and Stefanini (1952) describe a case in which the cells had to be washed six times before they could be transfused with safety.

In our case mild haemolytic reactions followed the use of whole blood. The severe and ultimately fatal reaction followed the use of thrice-washed packed cells. This may be due to the fact that in the case of the earlier transfusions the whole blood had been stored for several days before use, while the washed cells used for the final transfusion were prepared from freshly collected blood and given without delay. The heat-labile factor had probably deteriorated in the stored blood whereas the washed cells might have still retained traces of fresh plasma in which the heat-labile factor was active.

Haemochromatosis and Haemosiderosis. — Haemochromatosis signifies a condition in which there is an increase in the total iron content of the body accompanied by cirrhosis of the liver. Although skin pigmentation, diabetes, and other endocrine manifestations are present in many cases they are not essential for a diagnosis of haemochromatosis. Haemosiderosis, on the other hand, merely implies an increase in the total iron content of the tissues without altered function or morphology (Aufderheide et al., 1953).

Two types of haemochromatosis are recognized to-day: (1) a primary or endogenous type, and (2) a secondary or exogenous type. The aetiology of primary haemochromatosis is unknown, but anaemia is rarely present and there is a remarkable sex incidence of 20:1 in favour of the male sex. Secondary haemochromatosis has been found in association with prolonged anaemia, multiple blood transfusions, or both. Although these two types may be aetologically dissimilar their clinical and pathological manifestations are the same, and, as reference to the table below indicates, there is no essential difference in the distribution of the haemosiderin and haemofuchsin in the body tissue.

It is interesting to note that some cases of exogenous haemochromatosis show a similar dis-

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<td>COMPARISON OF PIGMENT DISTRIBUTION IN PRIMARY AND SECONDARY HAEMOCHROMATOSIS</td>
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++ = heavy deposition of the pigment, ++ = moderate deposition of the pigment, + = some excess of the pigment.

* The renal siderosis in our case is attributable to the paroxysmal nocturnal haemoglobinuria.

order of melanin metabolism as is seen in the primary form. Recently Nissim (1953) by parenteral administration of iron to animals has produced siderosis in sites which up to now have been exclusively confined to haemochromatosis. However, it has so far proved impossible experimentally to reproduce the disturbance of melanin metabolism seen in haemochromatosis of primary or secondary origin.

The total iron content of the body is about 5 g. of which about 2 1/2 g. is in the form of circulating haemoglobin in the red cells. In our case the liver alone contained 21 g. In addition there was a well-marked portal cirrhosis giving abnormal liver function tests. Thus she had the two essential criteria necessary for a diagnosis of haemochromatosis.

In view of her anaemia and sex it appears most likely that this is a case of exogenous haemochromatosis, although the coincidental existence of a primary haemochromatosis and paroxysmal nocturnal haemoglobinuria cannot be absolutely excluded.

Iron Loss and Storage in Paroxysmal Nocturnal Haemoglobinuria.—Superficially it might appear that the continuous intravascular haemolysis in this disorder should lead to the presence of a haemosiderosis. This, however, is not the case. The pattern, in the absence of massive and multiple transfusion therapy, is one of renal haemosiderosis associated with depletion of the normal iron deposits. This pattern is characteristic and specific and is in contrast to the other forms of chronic
haemolytic anaemia where the normal depots are full but the kidneys may contain little or no iron. The pattern of iron distribution seen is due to the almost constant haemosiderinuria which is characteristic of the disease. A daily loss of up to 5 mg. of iron may be incurred in this way, and when haemoglobinuria is present the total iron loss is much greater. Despite this loss patients with paroxysmal nocturnal haemoglobinuria are not generally iron deficient (Crosby, 1953), as there is a compensatory increase in iron absorption from the gastro-intestinal tract.

There are thus two points which require elucidation. The first concerns the aetiology of the haemosiderosis in a patient who was losing iron steadily through the kidneys for at least four years, and the second that of the portal cirrhosis.

Apart from primary haemochromatosis, to which reference has already been made, extensive haemosiderosis may be seen in patients who have received multiple and massive transfusion therapy (Schwartz and Blumenthal, 1948), or in patients suffering from malnutrition with pellagra (Gillman and Gillman, 1947).

That blood transfusion and "ferrivenin" therapy could not have contributed materially to the haemosiderosis is obvious from the fact that over the four years she was under treatment she received only 10 pints of blood, which would account for a mere 2.5 g. of iron and another 2.5 g. as "ferrivenin," whereas the liver alone contained 21 g.

Gillman and Gillman (1947) have described a condition of pigment cirrhosis in undernourished African natives. The liver pathology is indistinguishable from that seen in primary haemochromatosis. Our patient, however, showed no real evidence of general malnutrition, nor did her diet appear to have been inadequate or unbalanced.

Having excluded blood transfusion, "ferri- venin" therapy, and general malnutrition together or singly as sole factors in the aetiology of the haemochromatosis, we are forced to conclude that most of the iron must have been absorbed through the gastro-intestinal tract despite the fact that she did not require iron, as at no time was the anaemia a hypochromic one. Since normally, other than by haemorrhage, iron once absorbed cannot leave the body (Granick, 1954) the excess iron which was absorbed accumulated in the tissues, and caused a haemosiderosis and later a haemochromatosis.

Aufderheide et al. (1953) have reviewed the literature of exogenous haemochromatosis and have pointed out that the only common factor in all the cases described was the presence of a prolonged anaemia. They postulated that a prolonged anaemia causes a breakdown in the normal mechanism regulating iron absorption, leading to an excessive uptake of iron from the gastro-intestinal tract, even though the body does not require it. This iron accumulates and a haemosiderosis develops, and, if the patient lives long enough, portal cirrhosis and fibrosis in other organs may develop.

It is the degree and not the type of anaemia which is important. It may be macrocytic, microcytic, normocytic, aplastic, but, as long as the haemoglobin level remains low, iron will tend to be absorbed to excess. Studies with radioactive iron have shown that some anaemic patients continue to absorb appreciable quantities of iron though they do not require it (Dubach, Callender, and Moore, 1948). Experimentally the normal mechanism regulating iron absorption can be bypassed by massive doses of iron, low phosphorus intake, or both (Kinney, Hegsted, and Finch, 1949; Hegsted, Finch, and Kinney, 1949).

Our patient had a prolonged and severe anaemia, at times normocytic and at times macrocytic. She received large doses of oral iron (six to nine 3-gr. tablets of ferrous sulphate daily, almost continuously over a period of four years). Thus, the development of haemosiderosis in this case could be explained by the theory of excessive absorption of iron due to a chronic anaemic state, as in cases described by Aufderheide et al.

The aetiology of the portal cirrhosis is less obvious. The role of iron in the production of fibrosis is not as yet fully understood. Schwartz and Blumenthal (1948), with whom Aufderheide et al. agree, believe that the deposition of large amounts of iron in an organ or tissue will invariably induce fibrosis provided the patient lives long enough. Heitzman et al. (1953) and Norris and McEwen (1950) failed to find any constant relationship between the amount of iron deposited and the degree of fibrosis in an organ.

In the case under consideration it would appear that both the haemosiderosis and the portal cirrhosis may be explained on the basis of the prolonged and severe anaemia. The anaemia, by causing a local nutritional defect in the liver, may have initiated the portal cirrhosis, which in turn was accelerated and aggravated by the hepatic siderosis due to the increased absorption of iron from the gastro-intestinal tract. Thus a vicious cycle was set up which could only be broken by correcting the anaemia.
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These observations are not merely of theoretical interest, since if correct they would suggest that the prolonged administration of iron to patients who are not responding to it may lead to haemochromatosis. Most chronic haemolytic anaemias do not show evidence of iron deficiency, so that rational treatment should exclude that with oral or intravenous iron. If there is evidence that the iron depots are full, as indicated by a raised serum iron level and demonstrable iron in a marrow section, a diet limiting iron absorption should be considered. This may be achieved by giving a diet low in iron and high in phosphates, especially phytic acid, which renders the iron insoluble (Granick, 1954).

Megaloblastic Anaemia in Paroxysmal Nocturnal Haemoglobinuria and Haemochromatosis.—A macrocytic anaemia may be encountered in liver disease; it is, however, generally macronormoblastic and very rarely megaloblastic (Movitt, 1950). Koszewski (1952) noted the presence of a megaloblastic anaemia in nine cases of haemochromatosis in a series of 35.

Two years after this patient came under observation she developed a megaloblastic anaemia. Free acid in the stomach and a 93% fat absorption excluded Addisonian anaemia and steatorrhoea respectively. The anaemia showed a partial response to vitamin B₁₂ and liver extract, but complete remission only followed folic acid therapy. To what extent the paroxysmal nocturnal haemoglobinuria, by throwing an increased strain on the body's folic acid and vitamin B₁₂ reserves, was responsible for the development of a megaloblastic anaemia we are unable to say.

Conclusion

The diagnosis of paroxysmal nocturnal haemoglobinuria was somewhat delayed in this case as initially the haemolytic features were not evident. The cirrhosis of the liver and later the megaloblastic anaemia appeared to provide a satisfactory explanation for the signs and symptoms. However, following the detection of haemoglobinuria the special tests for paroxysmal nocturnal haemoglobinuria were carried out and the diagnosis soon confirmed. The most valuable and specific test is Crosby's modification of Ham's test.

The post-mortem findings of intense renal siderosis without significant splenic enlargement and marked hyperplasia of the red bone marrow were consistent with this diagnosis, as in no other disease is this intense renal siderosis seen.

The concomitant finding of hepatic cirrhosis with marked haemosiderosis and siderosis of other organs, which constitute a haemochromatosis, was quite unexpected. The significance of the previously unexplained bronze pigmentation of the skin was now obvious. Haemochromatosis was not considered during life, as its development in a condition such as paroxysmal nocturnal haemoglobinuria, which is associated with a daily iron loss, would appear illogical.

It is clear from this case that a chronic anaemia is capable of upsetting the normal mechanism regulating iron absorption from the gastrointestinal tract; if the cells of the intestinal mucus membrane are then presented with large quantities of absorbable iron much of it will be taken up, even though it is not required. It seems that in the presence of a prolonged anaemia of any kind the body is incapable of discriminating between an iron-deficiency and a non-iron-deficiency anaemia.

Summary

A case of paroxysmal nocturnal haemoglobinuria is described in which a fatal anaemia followed transfusion with washed blood cells.

At one stage the bone marrow showed megaloblastic erythropoiesis.

Necropsy revealed portal cirrhosis, intense siderosis of the liver and kidneys, and to a lesser extent of the spleen, pancreas, and other organs.

The mechanism for haemosiderosis is discussed in relation to current views on the regulating mechanism of absorption of iron from the gastrointestinal tract.

The part played by renal haemosiderosis in the production of kidney damage is discussed.

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A Case of Paroxysmal Nocturnal Haemoglobinuria Associated with Secondary Haemochromatosis, a Lower Nephron Nephrosis, and a Megaloblastic Anaemia

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