Isoniazid-resistant organisms were isolated at some time from about one-half the patients in the T1H and the T2H groups and from about two-thirds in the H group; but in the T5H group resistant organisms were obtained from only 3 out of the 10 patients, and in none before the end of the fifth month of treatment.

No oxytetracycline resistance was encountered.

There was no important difference between the four treatment groups as regards clinical or radiological progress over the first three months of treatment.

Treatment of one patient in the T5H group had to be stopped after one week because of intractable diarrhoea and vomiting. Apart from this, the toxic effects attributable to oxytetracycline were slight.

Owing to the considerable incidence of isoniazid resistance in the T1H and T2H groups, neither method can be recommended as satisfactory in treatment. On the other hand, oxytetracycline in a dosage of 5 g. daily would seem to be of probable value in delaying or preventing the onset of isoniazid resistance, but this combination is likely to be less effective than that of streptomycin or P.A.S. with isoniazid; it is also very expensive.

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ADDENDUM.—Since this paper was submitted for publication the patients reported above, and three additional patients in the T5H group, have completed a minimum of six months' clinical and bacteriological observation. The one exception was a patient in the T5H group who discharged himself from hospital after three months; the remainder of the cases in the T5H group completed six months' treatment. The figures for isoniazid resistance within six months of starting treatment (three-month figures in parentheses) are now: for isoniazid alone, 12 (11) out of 17; T1H, 5 (4) out of 10; T2H, 7 (3) out of 13; and T5H, 2 out of 12 (0 out of 13 at three months). The difference between the H and T5H figures at three months is statistically significant ($P < 0.01$). No oxytetracycline resistance was encountered.

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TREATMENT OF HAEMOCHROMATOSIS BY REPEATED VENESECTION

BY

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Repeated venesection is now being used in the treatment of haemochromatosis (Davis and Arrowsmith, 1953; Houston, 1953; Warthin *et al.*, 1953). It has been found that appreciable amounts of iron may be mobilized for haemoglobin formation in response to venesection and that the total amount of blood which can be removed without the development of anaemia is chiefly dependent on the available body iron store (S. Finch *et al.*, 1950). In haemochromatosis it is hoped by repeated bleeding to remove some of the enormous excess of iron deposited in the tissues and thereby halt the accompanying fibrosis and the clinical changes of the disease. The employment of venesection as a means of mobilizing the deposited iron in haemochromatosis is based mainly on theoretical considerations, and was first proposed by Balfour *et al.* (1942) and later by Schwartz and Blumenthal (1948) and by Granick (1949). The possible therapeutic use of venesection, however, is suggested by the rarity and late onset of haemochromatosis in women, in whom loss of iron through menstruation, pregnancy, and lactation is believed to suppress or delay the clinical expression of the disease (Houston, 1953).

A case of haemochromatosis, proved by skin biopsy and estimation of the serum iron and unsaturated iron-binding capacity (Houston and Thompson, 1953), has been treated by repeated venesection. During a period of two years 55 pints (31 litres) of blood, equivalent to approximately 15 g. of iron, have been removed. A severe anaemia developed at the end of this time and was preceded by a fall in serum iron, which suggested that the available body-iron stores had been exhausted. In spite of the anaemia, a definite improvement has been noted in the patient's condition.

Case Report

A man aged 55 came under observation in October, 1950, complaining of upper abdominal pain for two years, and increasing tiredness and pigmentation of the face for six months. He gave no family history suggestive of haemochromatosis and had had no previous illnesses other than an operation for duodenal ulcer in 1936. He had regularly drunk 6 to 8 pints (3.4 to 4.5 litres) of beer daily. On examination there was a marked grey-black pigmentation of the face, neck, and forearms, and the liver was enlarged and very tender, with a firm smooth edge palpable 4½ in. (12 cm.) below the right costal margin. The spleen was not felt, but free fluid was found in the abdomen, the abdominal girth being 44 in. (112 cm.). Examination of the urine revealed a mild glycosuria, but the liver-function tests and the blood count were completely normal. The diagnosis of haemochromatosis was established by skin

biopsy, which showed small scattered deposits of iron in the corium, particularly around the sweat glands.

He was admitted to hospital in October, 1950, December, 1951, and April, 1953, with exacerbation of upper abdominal pain, and on each occasion was reinvestigated and discharged after the pain had been relieved by a suitable period of rest. The glycosuria, which was present on repeated examination in 1950, was not found in 1951 or 1953, and the glucose-tolerance test, which was reported as being of the "lag type" in 1950 and 1951, was normal in 1953. The serum-protein and liver-function tests have been normal at each examination. Apart from the onset of impotence in 1950, the patient's condition remained more or less stationary throughout this time, and no further abnormality was discovered in any other system.

Withdrawals of 1 pint (570 ml.) of blood weekly by venesection were started in April, 1952, and were carried out in two series—the first from April to November, 1952, and the second from April to October, 1953. In the first series 35 pints (20 litres) of blood were removed without ill effect, the haemoglobin ranging from 13 to 16.3 g. per 100 ml.

Serum iron and unsaturated iron-binding capacity estimations were begun in March, 1953, just before the start of the second series of venesections. The serum iron was estimated by the method of Ramsay (1953) and the unsaturated iron-binding capacity by the method of Ventura (1952). Both methods were found to be satisfactory and reliable provided care was taken to prevent any haemolysis of specimens. The iron-free distilled water used in these estimations was obtained by running distilled water through a 4-foot (120-cm.) column of Biodeminrolit ion-exchange resin. The normal value for serum iron as given by Ramsay is 112–255 μ g. per 100 ml. in males; Ventura found the serum unsaturated iron-binding capacity to be within the range 198–470 μ g. per 100 ml. The initial finding of a serum iron of 286 μ g. per 100 ml. and a fully saturated iron-binding capacity was confirmatory of the diagnosis of haemochromatosis (Houston and Thompson, 1953). The complete results, together with haemoglobin estimations, are shown in Fig. 1.

FIG. 1.—Serum iron, serum unsaturated iron-binding capacity, and haemoglobin estimations from April, 1953, to March, 1954.

In the second series of venesections 20 pints (11 litres) of blood were removed. After 10 pints (5.5 litres) of blood had been withdrawn the serum iron began to fall and did so progressively until in October, 1953, the lowest figure of 22 μ g. per 100 ml. was recorded. The haemoglobin, which was 12.7 g. per 100 ml. at the start of the second series of venesections, fell slightly, but it was not until October, 1953, that the haemoglobin suddenly dropped to 8.2 g. per 100 ml., the anaemia being hypochromic normocytic in type. At this time the patient became increasingly dyspnoeic and was admitted to hospital for a short period. The venesections were discontinued, but the serum iron remained at an abnormally low level and the haemoglobin showed only a slow increase to 11.5 g. per 100 ml.

From the start of the second series of venesections in April, 1953, the patient began to feel better in himself and was less tired. In October he resumed work for the first time for nine months in spite of the shortness of breath consequent upon the development of anaemia. The shortness of breath has since gradually improved, and at the time of writing he stated that although he was still troubled by abdominal pain he felt better than at any time since he first became ill. On examination the pigmentation of the face and neck was noticeably less and that of the forearms had almost disappeared. The liver was palpable 4½ in. (11.4 cm.) below the right costal margin, but was much less tender, and no free fluid could be detected in the abdomen. The abdominal girth was 39 in. (99 cm.), as compared with 44 in. (112 cm.) in 1950. The glycosuria, which was present in 1950, was not found on any subsequent occasion.

Discussion

A fall in serum iron and the development of a severe anaemia as the result of the treatment of haemochromatosis by repeated venesection has not previously been recorded. Under normal conditions the serum iron reflects the level of iron available for haemoglobin synthesis (Granick, 1949) and the combination of low serum iron and high unsaturated iron-binding capacity is characteristic of iron-deficiency anaemia (Rath and Finch, 1949). The pronounced fall in serum iron preceding the development of a severe anaemia therefore suggests a progressive depletion followed by complete exhaustion of the iron available for haemoglobin synthesis.

It is, however, unlikely that the 15 g. of iron removed represents the total iron stores of the body, as this has been estimated to be between 25 and 50 g. in haemochromatosis as compared with 3–5 g. in the normal person (Sheldon, 1935). It is possible that in the present case some of the iron may have been deposited in the form of very large aggregates of haemosiderin that are only slowly mobilized, especially if they have been deposited extracellularly or in such amounts as to interfere with cell function, as suggested by C. A. Finch *et al.* (1950). In other cases of haemochromatosis treated by venesection similar amounts of iron have been removed without the development of significant anaemia, and in the cases reported by Davis and Arrowsmith (1953) serial biopsies have shown pronounced diminution, and in one case almost complete disappearance of iron from the liver. These authors also quote one patient in whom 103 litres of blood, equivalent to 52 g. of iron, were removed without untoward effect.

The persistence of the anaemia raised the problem of whether iron should be given in an attempt to increase the rate of blood regeneration. It was expected that on discontinuing venesections the absorption of iron from the diet would lead to an increase in haemoglobin concentration at least as rapid as that occurring in a successfully treated iron-deficiency anaemia, and that it would be followed, as the iron stores were replaced, by an increase in the serum iron. The haemoglobin, however, showed only a very slow increase, and the serum iron remained consistently low. The possibility of a defect in absorption therefore had to be considered. An oral-iron-absorption test showed adequate absorption of a 45-gr. (3-g.) dose of ferric ammonium

citrate (Fig. 2), and it was concluded that the persistence of the anaemia was due to the deficiency of iron in the diet. It was nevertheless decided to refrain from giving additional iron on the grounds that the patient was not unduly disturbed by the anaemia and that the administration of iron seemed a contradiction of the previous treatment.

FIG. 2.—Oral-iron-absorption test.

The important question of the relationship between the accumulation of excess iron in the tissues and the development of haemochromatosis has not been fully elucidated (Althausen *et al.*, 1951). It has not been demonstrated that the accumulation of iron in the form of ferritin and haemosiderin by itself will bring about cell destruction with consequent fibrosis, and it is probable that the process by which iron is deposited in haemochromatosis is a physiological one. The suggestion has therefore been made that it is the iron that cannot be converted into ferritin, either because of too rapid deposition or because the tissues are already saturated, which brings about cell destruction either by the precipitation of proteins or by the inactivation of specific enzymes (Granick, 1949). This is in accord with the observations of Bothwell *et al.* (1952), who investigated two patients, one a male and one female, both of whom were in their early twenties and had severe heart failure. Radio-iron-absorption studies showed an increase of absorption of iron in these patients as compared with four other subjects with haemochromatosis, who themselves had uptakes greater than normal. The disease appeared to be in a more acute form in the two younger patients and the damage to the myocardium to be related to the rate of deposition of iron rather than to the actual amount of iron which was being laid down. The possible effect of venesection may therefore depend not so much on the quantity of iron removed as upon the stage the disease has reached by the time treatment is begun.

Owing to the rarity of haemochromatosis the number of patients so far treated is small, and any assessment is necessarily tentative and incomplete. Houston (1953) and Warthin *et al.* (1953) reported individual cases, the latter's showing considerable improvement, and in our own case definite subjective and objective improvement was noted. Davis and Arrowsmith (1953) have collected 30 cases treated by venesection, with details of 15, of whom 12 are reported as showing a satisfactory response to prolonged repeated bleeding. In a series of the patients personally seen by Davis and Arrowsmith since 1945, six were adjudged to be suitable for bleeding and four were excluded because of carcinoma of the liver, carcinoma of the prostate, and severe anaemia. Of the six patients treated by venesection one has died, four have had favourable responses, including two who showed striking improvement, and one, treated

cautiously because of congestive heart failure, has had treatment too recently for evaluation. Thus, though some of the results achieved are encouraging, it appears that treatment by repeated venesection is limited to a selected group of cases. In addition, Davis and Arrowsmith have pointed out the burden of repeated venesection, which is such as to make it difficult or impossible to persuade some patients to undertake or continue treatment. This difficulty did not arise in our patient, who was very co-operative throughout the whole period of venesection.

The assessment of venesection in terms of prognosis and its eventual place in the treatment of haemochromatosis will require prolonged and careful observation. Since Sheldon's (1935) estimate of 18 months as the average duration of life from the diagnosis of haemochromatosis, considerable advances have been made in the treatment of diabetes and cirrhosis of the liver, with consequent improvement in prognosis. Marble and Bailey (1951), for example, found the average duration of diabetes in 30 cases of haemochromatosis recognized since 1922 to be 4.9 years, and the duration of diabetes in three living cases, with an average age of 64, to be 9.2 years. At the same time it must be remembered that other complications such as cardiac failure and primary carcinoma of the liver, the incidence of which is very much greater in haemochromatosis than in cirrhosis of the liver (Warren and Drake, 1951), may well become more apparent as age increases. The age of the patient and the duration of the disease before starting treatment may, moreover, be found to be important factors determining the prognosis and the effectiveness of venesection.

Since the advent of the diagnosis of haemochromatosis by liver biopsy and serum-iron estimations, it has become possible to make a diagnosis before the full clinical picture of pigmentation, diabetes mellitus, and cirrhosis of the liver has developed. It has, as a consequence, been advocated that the disease should be recognized as early as possible—for example, on a single finding such as hepatomegaly (Feder *et al.*, 1950)—and that treatment should be started before irreversible changes have occurred. Whether this will materially alter the prognosis or the effectiveness of venesection is not known. From the reports so far published, it seems established that some patients do show initial improvement as the result of treatment by repeated venesection, and the impression has been gained that patients are permanently benefited and their lives prolonged.

Summary

A case of haemochromatosis treated by repeated venesection is reported. A total of 55 pints (31 litres) of blood was removed over the course of two years. At the end of this time a severe anaemia developed which is believed to have been due to exhaustion of available iron stores.

Some subjective and objective improvement has taken place in spite of anaemia, and the published reports suggest that venesection is an effective means of treating selected patients with haemochromatosis.

ADDENDUM.—When the patient reported on above was last seen on November 9, 1954, his haemoglobin was 15 g. per 100 ml., serum iron 156 µg. per 100 ml., and unsaturated serum iron-binding capacity 331 µg. per 100 ml. His only complaint was of aches and pains in the joints, and his physical signs remained unchanged.

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PURE RED-CELL ANAEMIA IN PATIENTS WITH THYMIC TUMOURS*

BY

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Selective bone-marrow aplasia involving erythropoiesis and leaving leucocyte and platelet production unaffected is most uncommon, being referred to by Whitby and Britton (1953) as a rare curiosity and mainly of theoretical interest. This disorder was first described by Kaznelson (1922), who called it erythrophthisis. Reports of the condition occurring both in children and in adults are now more frequently seen, and long-term studies are being made (Diamond, 1954).

The cause of this type of anaemia remains unknown. A congenital origin, ABO blood-group incompatibility between mother and affected child, allergy, riboflavine deficiency, toxins, and "hypersplenism" have all been suggested as possible explanations by various writers, and there may be a mixed aetiology underlying the unusual bone-marrow change leading to "pure red-cell anaemia," the term first used by Lescher and Hubble (1932).

A syndrome of selective erythroblastic aplasia in association with the presence of a thymic tumour has been observed in a proportion of the small number of adult cases which have been fully investigated. Davidsohn (1941) recorded the case of an adult woman with severe anaemia due to erythroid hypoplasia who was found at necropsy to have a lympho-epithelioma of the thymus. The case reported by Humphreys and Southworth (1945) and that of Chediak *et al.* (1953) both showed prompt haematological improvement after removal of thymomas. Ross *et al.* (1954), with whom we have had exchange of information for some time, record two cases showing the simultaneous occurrence of benign thymoma and refractory anaemia very comparable to those described in this paper. Removal of thymoma in both of their cases—and also splenectomy in one of them—was not followed by any haematological improvements.

This preliminary report gives abridged case histories of two adult patients with pure red-cell anaemia. One of them also had myasthenia gravis. Both had thymomas and were subjected to thymectomy, splenectomy,

and A.C.T.H. therapy, with ultimate recovery. Further details, discussion, and follow-up studies will be published elsewhere.

Case 1

An electric-train driver aged 48 was transferred from the National Hospital for Nervous Diseases on June 28, 1951, for investigation of severe anaemia. Weariness, dyspnoea, and palpitation had increased progressively for a month. Dr. Denis Williams had some eighteen months previously diagnosed myasthenia gravis and the patient had been treated with oral neostigmine, belladonna, and ephedrine with excellent clinical effect. His history disclosed no apparent cause for the anaemia. He had been married for twenty-five years and had a family of three. For about six years there had been gradual loss of libido.

On examination he was a cheerful, heavily built, thick-set man—height 5 ft. 9 in. (175 cm.); weight 12½ st. (79 kg.)—showing marked pallor of the skin and mucous membranes. The heart rate was 80 and regular, there being a systolic murmur over the praecordium. His B.P. was 130/60. Clinical examination of lungs and nervous system was negative, myasthenia being controlled with neostigmine. The tongue was normal and no abdominal mass or palpable enlargement of liver or spleen was present.

Investigations and Progress

Blood examination showed severe normochromic anaemia with red cells varying little in size and shape and showing no polychromasia: Hb, 27% (4 g.); red cells, 1,340,000 per c.mm.; C.I., 1; P.C.V., 11.5%; M.C.V. 85 cubic μ ; M.C.H.C., 35%; white cells, 5,200 (polymorph neutrophils 49%, lymphocytes 47%, monocytes 4%, eosinophils nil); platelets 325,000 per c.mm. No reticulocytes or nucleated red cells could be found on repeated examination. Blood group: A, Rh (D) positive, direct Coombs test negative, bilirubin less than 0.5 mg. per 100 ml.; blood urea, 21 mg. per 100 ml.; thymol turbidity, 1.2 units; alkaline phosphatase, 3.4 King-Armstrong units; serum proteins, 6.9% (albumin 3.4 g.%, globulin 3.5 g.%; A.G. ratio 1:1); normal red-cell fragility, bleeding-time, clotting-time, and clot retraction. Wassermann reaction and Kahn test were negative. An alcohol histamine test meal showed no free hydrochloric acid in the gastric juice, but retesting later showed free acid to be present. The urine was normal and contained no excess urobilinogen.

Smears of sternal marrow showed average cellularity with a striking absence of all forms of erythroblasts. Only a very occasional equivocal red-cell precursor could be found, but a large number of small densely staining cells with little or no cytoplasm were seen. These were regarded as probably of lymphoid type. A slight increase in plasma and reticulum cells was observed. Myeloid series and megakaryocytes seemed of normal morphology and distribution.

Transfusion of concentrated red cells derived from approximately 2,000 ml. of citrated blood gave benefit. The blood count figures rose to Hb 46% (6.8 g.), red cells to 2,000,000, and P.C.V. to 18%. No reticulocytes could be found.

While tomography was not performed in this case, there was no good evidence of mediastinal tumour on the plain x-ray film of the chest. Treatment for myasthenia gravis with oral neostigmine, 15 mg. q.d.s., together with belladonna and ephedrine, was continued. No haematological benefit was obtained from prolonged treatment with various haematinics. A course of intramuscular A.C.T.H. (1,425 mg. over two weeks) also caused no change in the marrow or blood findings, reticulocytes being consistently absent. Repeated blood transfusions seemed the only means of keeping the patient alive.

After reading the remarkable case recorded by Humphreys and Southworth (1945), in which removal of a tumour of probable thymic origin appeared to have a direct influence on pure red-cell anaemia, we were led to consider this operation for our patient. It was also possible that this

*A description of these cases was given by Dr. Chalmers at the Fifth International Congress of Haematology, held in Paris in September, 1954.