THE DIFFERENTIAL DIAGNOSIS AND TREATMENT OF SEVERE ANAEMIA *

BY

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Twice in comparatively recent years has anaemia been the subject of discussions at Annual Meetings of the British Medical Association. At Edinburgh in 1927 Professor Gulland opened a discussion on "The Pathology and Treatment of Pernicious Anaemia," and was followed, among others, by Drs. Minot and Murphy (of Boston) with a paper describing their success in the treatment of pernicious anaemia with "a diet rich in liver," of which they had first published an account in America in the previous year. The striking developments since then—the practical isolation of the pernicious anaemia factor in both liver and stomach extracts, and the remarkable results obtained in the treatment of a disease previously regarded as hopeless—furnish ample justification for the prominence which is being given to the subject this year in Melbourne. In 1931, at Eastbourne, a discussion on "The Varieties of Secondary Anaemia and their Treatment" was opened by Dr. L. J. Witts with a paper entitled "Chronic Microcytic Anaemia."

Classification of Anaemias

In undertaking the responsible task of opening this discussion on "severe" anaemia, I am confronted by the length and complexity of the modern classification of the anaemias, any one of which may be "severe" at some stage of its development. In order to avoid confusion and to concentrate attention on essentials I suggest that for the present purpose the following classification will serve:

1. Pernicious anaemia.
2. Idiopathic hypochromic anaemia.
3. Other deficiency anaemias—for example, scurvy, myxoedema.
4. Anaemias characterized by haemolysis—acholuric jaundice, anaemias due to chemical poisons, etc.
5. Anaemias secondary to: (a) malignant disease, especially that of the alimentary tract; (b) infections; (c) haemorrhage, acute and chronic.
6. Aplastic anaemia.
7. Splenic anaemia.

It will be agreed that it is to (5) alone that the word "secondary" is really applicable; nevertheless it has been the custom to apply it to all microcytic anaemias, and even to permit the use of the contradictory term "idiopathic secondary anaemia."

Differential Diagnosis: Three Questions

I propose to discuss the differential diagnosis by putting and partly answering the following questions:

1. Can a provisional diagnosis be reached by consideration of the history, symptoms, and ordinary clinical signs alone?
2. How much further can the diagnosis be carried by the use of such simple haematological methods as are within the scope of general practice?
3. To what extent is the further information that can be obtained by investigations at the hands of an expert clinical pathologist necessary not only in determining the exact diagnosis but also in guiding treatment?

Question 1

A careful review of the ordinary clinical data can, in many cases, carry the differential diagnosis quite a long way; in some of these a conclusion can be reached such as would justify the adoption of a specific line of treatment, especially when a confirmatory report by a haematologist is not easily available. The description, which follows, of certain clinical features of some of the anaemias is intended to illustrate this point; that it is very incomplete is admitted.

Although the onset of pernicious anaemia is so insidious that the patient has difficulty in fixing a date to his first symptoms, inquiry will usually elicit information pointing to the probability that the disease has not been in progress more than twelve months at the outside prior to his first request for medical advice. The symptoms have been those common to all varieties of anaemia, together with digestive discomfort—vague dyspepsia, diarrhoea, constipation, or occasional vomiting—on the one hand, or nervous symptoms due to involvement of posterior and lateral tracts on the other. Yet, in spite of these symptoms and of the obvious presence of a severe degree of anaemia, the patient may have remained at work; in this respect there is a contrast with other forms of anaemia. There is never any real loss of weight—the combination of this feature with extreme pallor is proverbially diagnostic. Soreness of the tongue occurs in a number of cases, but is not pathognomonic as it was once thought to be, as it is found in other forms of anaemia. On the other hand, although actual glossitis is absent in many cases, it can be stated definitely that in all cases of pernicious anaemia "fur" is conspicuous by its absence. The spleen is often just palpable, but gross enlargement is suggestive of some other diagnosis. The presence of symptoms and signs of subacute combined sclerosis points strongly to the diagnosis of pernicious anaemia. The position may be put dogmatically: where anaemia is combined with a very long history, loss of weight (even if only moderate), gross splenomegaly, and/or furred tongue, the condition is not pernicious anaemia.

Idiopathic hypochromic anaemia (simple achlorhydric anaemia, chronic microcytic anaemia) occurs almost exclusively in women; its age distribution differs little from that of pernicious anaemia. The history is usually one of many years of vague ill-health, without the progressive deterioration which is, albeit with temporary intermission, characteristic of pernicious anaemia. For a description of the clinical features I quote Piney's "free" translation of Kaznelson and Weiner:

Medical advice is sought for various reasons; often symptoms due to anaemia are particularly noticeable, such as palpitation, pallor, fatigue, fainting attacks, and pains in the bones. Diarrhoea and loss of appetite may be due to the achlorhydria, even when anaemia is only of moderate severity. No changes other than those dependent on the anaemia are found in the internal organs. Lingual changes of the nature of Hunterian glossitis are common. Nervous symptoms, such as paraesthesiae, occur; and one of the most striking signs is an alteration in the nails of the hands and feet. These are hollowed (koilonychia or spoon nails); in addition, the nails are tender and brittle.

Some cases show the combination of anaemia, glossitis, and dysphagia often known as the Plummer-Vinson syndrome. Other cases exhibit mild mental abnormalities suggestive of neurasthenia.

The diagnosis of either of these forms of primary anaemia from anaemias secondary, on the one hand to occult chronic blood loss, and on the other to cancer of the alimentary tract, may be practically impossible on

* Read in opening a discussion in the Section of Medicine at the Annual Meeting of the British Medical Association, Melbourne, 1935.

simple clinical examination, but there should be little difficulty in selecting the cases for which x-raying of the alimentary tract or full haematological investigation is necessary.

Aplastic anaemia occurs rather more frequently in women than in men; its age incidence is younger than that of the above. The onset is insidious but fairly rapid; the first complaints are those usually associated with any anaemia; the patient is extremely pale and the sclerotics are bluish-white. As the condition develops, petechiae and other haemorrhagic phenomena occur, and stomatitis may become very intense. There is no splenomegaly.

The conditions (probably more than one) covered by the terms "splenic anaemia," "Banti's disease," etc., occur usually in young adults. The spleen enlarges progressively—palpable even in early cases, very large in later ones; splenic enlargement may be discovered for the first time during a routine medical examination for life insurance or in connexion with ordinary simple illness. The disease is essentially chronic; the anaemia is moderate in degree, except as the immediate sequel of haematemesis, which occurs sooner or later in most cases.

Question 2

Can the family practitioner advance the diagnosis a stage further without recourse to the expert clinical pathologist?—an important practical consideration, in view of the frequency of anaemia among all classes and the comparative scarcity of the expert at a distance from the larger centres. The student is taught the use of the haemocytometer and the haemoglobinometer in the wards of his hospital, but I fear that the majority fail to attain the degree of dexterity at which the use of these instruments ceases to be drudgery and the findings become reliable; a few carry their experience into general practice, and undertake at least a preliminary haematological survey of their cases of anaemia. The one outstanding criterion for treatment being the recognition of a megalocytic* from a microcytic anaemia, I am surprised that so little use is made of the halometer (Eve's or other pattern), of the value and reasonable accuracy of which there can be no doubt. It is remarkable how little reference to its usefulness is made in recent books on haematology. I am glad to know that a later speaker in this discussion proposes to elaborate this point.

The value and simplicity of the chemical test for urobilin in the urine need only be mentioned to be appreciated.

Question 3

In spite of what might be inferred to the contrary from the foregoing there is no doubt that the answer to my third question must be in the affirmative. A haematological investigation by an expert is of the greatest value not only in diagnosis but also in the control of treatment, if the best possible progress is to be obtained. Constant practice enables him to achieve a degree of technical dexterity and diagnostic experience such as the practitioner has neither the time nor the opportunity to acquire. This applies to some extent to such comparatively simple procedures as blood counts and haemoglobin estimation, but more particularly to the following:

(a) Reticulocyte counts, of special value as an index of response to treatment in cases of pernicious anaemia, providing at once a guide to further dosage of liver preparations, confirmation (or otherwise) of the diagnosis, and data on which a prognosis may be based.

(b) Enumeration of blood platelets, necessary in the diagnosis of anaemias characterized by purpuric manifestations or by splenomegaly.

* "Megalocytic," rather than "macrocytic," to avoid confusion with "microcytic," especially in speech.

(c) Differential counts of the leucocytes, including the recognition of immature forms, such as are found in unusual types of leukaemia, to which the anaemia may be secondary.

(d) Estimation of the fragility of the red cells.

Specific Treatment

There is probably no group of conditions where a positive diagnosis points the way to the appropriate and specific treatment more directly than in the anaemias. It is unfortunate, to say the least, that during the years that have followed the discovery of liver therapy the doctor's mail has been flooded with advertising slips and pamphlets advocating the use of liver preparations, not only for pernicious anaemia, but also, in various combinations, for any type of anaemia. Without animadverting on the indiscriminate prescription of liver, which has been the vogue, I venture to suggest that it will now be generally agreed that liver preparations are effective in megalocytic anaemias alone, and that their use for other conditions is to be deprecated as unscientific and uneconomic. On the other hand, whilst iron is a specific for idiopathic hypochromic anaemia, and very valuable in the treatment of other microcytic anaemias, it must be remembered that in a few cases of pernicious anaemia iron is required in addition to liver if the optimum result is to be obtained. (The use of liver and stomach extracts is to be the subject of a separate contribution to the discussion.)

It is only in recent years that the value of iron in large doses has been fully realized. There is ample evidence that the increase of the dose of 30 grains of ferri and ammon. cit. to 120 or even 240 grains per day makes the difference between failure and success, and that the larger dose is well tolerated. There is no advantage in using organic preparations; subcutaneous or intramuscular injections are valueless, because the dose is necessarily much too small. The addition of a small dose of copper (1/48 grain of the carbonate) to each dose of iron has been advocated, but has not so far met with general adoption.

As regards the prescription of hydrochloric acid to cases with achlorhydria or hypochlorhydria, its practical value seems to prove to be much less than, on theoretical grounds, might be expected. Severe cases of pernicious anaemia cannot tolerate it at all, and milder cases take it, however disguised, under protest. Its routine use, therefore, cannot be justified; in a few cases it seems to aid digestion, especially if whole liver is being taken. In other anaemias with absent or deficient HCl evidence of its value is somewhat conflicting.

Of the outstanding advantage to be gained by transfusion of whole blood in suitable cases there is, of course, no doubt. In aplastic anaemia transfusion at regular intervals is essential to life, and in some cases permits a moderate degree of activity. Its use in the severe crises of pernicious anaemia has been much less frequent in recent years as the result of the availability of active liver extracts for intravenous administration. However carefully the bloods of donor and recipient have been "matched," there seems an excessive tendency to the production of severe reactions.

Points for Further Discussion

The following questions suggest, *inter alia*, some points for discussion:

What are the minimal criteria on which diagnosis can be based?

Once the diagnosis has been established, what are the disadvantages and risks of treatment without haematological control?

Why need iron be given in such large doses to secure the absorption of the small amount necessary?

Does copper or other metal assist improvement?

For what type of case is blood transfusion a real necessity?