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CLINICAL PICTURE OF PERNICIOUS ANAEMIA PRIOR TO INTRODUCTION OF LIVER THERAPY IN 1926 AND IN EDINBURGH SUBSEQUENT TO 1944

BY

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Thirty years have elapsed since Minot and Murphy (1926) published their historic report on the value of liver in the treatment of pernicious anaemia. With each passing year fewer and fewer physicians remain on the staffs of the teaching hospitals who have had personal experience of the clinical features and course of pernicious anaemia in the era prior to the introduction of liver therapy. During the period 1920-7, first as assistant and then as a lecturer in the Department of Medicine, University of Edinburgh, I had ample opportunity of observing the tragic and inevitably fatal termination of the disease in large numbers of patients admitted to the wards of the Royal Infirmary under the charge of my chief, Professor G. L. Gulland, a famous haematologist.

I believe that the number of persons suffering from pernicious anaemia at the present time is much greater than it was when I first became interested in the disease 36 years ago. Hence the importance of early and correct diagnosis. There are two main reasons for this increased incidence. Firstly, the introduction of liver extract and later of vitamin B₁₂ has enabled patients suffering from Addisonian pernicious anaemia to have a normal expectation of life. Secondly, at the present time there are many more people in the world within the age group 60-80 than there were at the beginning of the twentieth century, and therefore the number of persons who are liable to develop Addisonian pernicious anaemia is correspondingly greater. It has also seemed to me that certain clinical features present in the late stages of pernicious anaemia in the pre-liver era occurred so frequently and were so striking in character that they have continued to be reported as being of considerable diagnostic value, when in reality they are now of very limited importance in this respect.

Before this view could be accepted it would be necessary to demonstrate that the clinical picture of pernicious anaemia at the present time is in fact different from that seen prior to the discovery of liver therapy. Accordingly, I examined the records of 250 cases of pernicious anaemia which had been under my charge in Edinburgh during the period 1944-56 and compared them with the clinical features recorded in patients investigated prior to 1926: (1) by Davidson and Gulland (1930) in Edinburgh; (2) by Richard C. Cabot (1908) (in preparing this article Cabot stated that he had studied the case records of (a) 337 patients under his charge in

private and hospital practice, (b) 320 case records collected from his medical friends in different parts of America, and (c) 543 cases selected by him after critical study of the literature, making a total of 1,200 cases); and (3) by Panton, Maitland Jones, and Riddoch (1923), who analysed 117 cases of pernicious anaemia admitted to the London Hospital between 1911 and 1920.

Age of Onset and Duration of Symptoms

Fig. 1 clearly shows that the age of onset of the disease is much later at the present time than it was 50 years ago. Thus more than 50% of the patients in the Edinburgh

FIG. 1.—Age of onset.

series (1950-6) developed the disease when over 60 years of age, as compared with only 10% in Cabot's series (1908). There can, however, be little doubt that this figure of 10% underestimates the true incidence. Cabot states that he included in his series 35 cases of the megaloblastic anaemia associated with pregnancy, a condition which develops in young women. In addition, some cases of the megaloblastic anaemia due to malabsorption must have been mistaken for Addisonian pernicious anaemia. Lastly, since diagnosis was much less accurate 50 years ago than it is at the present time, it would seem probable that the inclusion of cases of macrocytic anaemia due to aplastic, haemolytic, or leukaemic disease was partly responsible for the high incidence of "pernicious anaemia" stated by Cabot to occur under the age of 40 years.

TABLE I.—Duration of Symptoms

	Pre-Liver Series		Edinburgh Series 1944-56 Davidson 250 Cases
	1908 Cabot, Boston 1,200 Cases	1923 Panton, London 117 Cases	
Duration of symptoms before medical advice was sought	"Disability extending back for years"	Average 17 months	26% < 3 mths. 56% < 6 mths. 75% < 12 mths.

Table I indicates that the duration of symptoms prior to diagnosis is much shorter to-day than it was in the pre-liver era. Cabot states that many of his cases had symptoms

"extending back for years," and Panton states that the "average duration of the illness was 17 months prior to admission to hospital." Symptoms had been present for less than six months in 50% of the Edinburgh series (1944-56) and under one year in 75% of the cases.

Sex Incidence

Fig. 2 shows that in Cabot's series (1908) the disease affected males twice as often as females, whereas in an Edinburgh series of 600 cases seen during the period 1938-56

FIG. 2.—Sex incidence.

females were affected twice as often as males. A recent analysis of 223 cases examined in Glasgow showed an incidence of three females to one male (personal communication from Professor L. J. Davis). Wintrobe (1951) states that in the United States of America and in England males have been more frequently the victims of this disease than females, but in Germany and the Scandinavian countries the opposite has been recorded.

Symptoms

All authorities agree that the onset of the illness in the great majority of cases of pernicious anaemia is extremely insidious. This is as true to-day as it was 50 years ago. Patients continue to work for a surprisingly long time after the development of the disease before consulting their doctors. In addition, the anaemia is often much more severe than would be expected by the appearance of the patient or from a study of his symptoms. Table II shows

TABLE II.—Symptoms

	Pre-Liver Series		Edinburgh Series 1944-56 Davidson
	1908 Cabot, Boston	1923 Panton, London	
No. of cases	1,200	117	250
Weakness and tiredness	96%	91%	90%
Dyspnoea	88%	—	70%
Sore tongue	43%	24%	25%
Diarrhoea	(of 372 cases) 51%	(of 34 cases) 26%	9%
Constipation	35%	—	16%
Paraesthesiae	100%	—	38%

that the two symptoms most commonly encountered in pernicious anaemia, both in the pre-liver era and at the present time, are *general weakness and tiredness*, and *dyspnoea on effort*. The third most frequent symptom is the feeling of numbness and tingling in the hands and feet (*paraesthesiae*). This symptom, however, occurs much less frequently now (38% of cases) than it did 50 years ago (approximately 100% of cases), as indicated in Table II. This is also true of *soreness of the mouth and tongue*, which was present in 25% of the Edinburgh series as compared with 43% of Cabot's series. Davidson and Gulland (1930) stated that this feature was present in approximately half of their cases.

While indefinite symptoms referable to the digestive tract, such as poor appetite and vague abdominal discomfort, are frequently encountered in patients with pernicious anaemia, *diarrhoea* occurred in only 9% of the Edinburgh

series. This is in marked contrast to Cabot's series, in which it was a notable feature in 51% of cases. Davidson and Gulland (1930) also state that *diarrhoea* occurred in approximately half of their cases at some stage of the illness. At the present time the complaint of constipation is twice as frequent as that of *diarrhoea*.

Signs

Apart from *pallor* of the mucous membrane and the skin, the most common finding in the Edinburgh series was a *pale smooth tongue* which was also moist and very clean. This was noted in no less than 64% of cases (see Table III).

TABLE III.—Signs

	Pre-Liver Series		Edinburgh Series 1944-56 Davidson
	1908 Cabot, Boston	1923 Panton, London	
No. of cases	1,200	117	250
Fever	79%	71%	22%
"Icterus"	Most cases	—	Uncommon
Acute glossitis (red and ulcerated)	42% (of 372 cases)	—	5%
Chronic atrophic glossitis (pale and smooth)	—	—	64%
Splenomegaly	27%	18%	8%
Spinal cord damage	11%	—	7%
Ataxic type	7%	—	6%
Spastic type	4%	—	1%
Peripheral blood:			
< 2 million R.B.C./c.mm.	86%	Average	58%
< 1 million R.B.C./c.mm.	21%	1.39 million	1%

No percentage figure for this sign is available in Cabot's or Panton's series, nor in Davidson and Gulland's monograph (1930). An extraordinary cleanness of the tongue in pernicious anaemia has, however, been mentioned by many authorities as being a common feature, and this sign is undoubtedly the result of atrophy of the papillae and mucous membrane of the tongue (*chronic atrophic glossitis*). *Acute glossitis*, indicated by a beefy-red, painful, and often ulcerated tongue, was reported as being present in patients in the pre-liver era in up to 50% of cases, in contrast to only 5% of the Edinburgh series. The second most common sign in the Edinburgh series was *fever*, which was present in 22% of the cases, in contrast to 79% in Cabot's series. The frequency and degree of fever is related to the severity of the anaemia, and the pyrexia disappears when the blood supply to the heat-regulating mechanism of the brain is improved by blood transfusion or as a result of treatment.

Icterus was another sign to which much attention was paid in the pre-liver era. Cabot rightly says that it is doubtful if the waxy yellow colour of the skin, which is such a notable feature of pernicious anaemia in severe relapse, is actually due to jaundice. Be that as it may, I am certain that this appearance of the skin is much more rarely seen at the present time than it was in the era before the discovery of liver therapy.

Minor degrees of *splenomegaly*—that is, the tip of the spleen being just palpable below the costal margin—were common in the pre-liver era. According to Cabot the spleen was palpable in no less than 27% of cases, but in the Edinburgh series it could be felt in only 8%. Gross enlargement of the spleen is so uncommon in pernicious anaemia that its presence should give rise to suspicion that the diagnosis is incorrect.

The *neurological features* of pernicious anaemia have always excited much interest. The name subacute combined degeneration of the cord was adopted to describe the lesions of the posterior and lateral columns of the cord which were so commonly present in patients dying of pernicious anaemia in the pre-liver era. The name is unsatisfactory in that the disease usually starts insidiously and not subacutely, combined lesions are often absent, and no cognizance is taken of the fact that lesions of the peripheral nerves occur much more frequently and much earlier than lesions of the central nervous system. If the name subacute

combined degeneration of the cord is to be retained it would appear logical to limit its use to lesions of the central nervous system. Unfortunately, even neurologists find it difficult to decide on the clinical features which clearly distinguish lesions of the posterior columns of the cord from lesions of the peripheral nerves. It is generally agreed that tendon reflexes, vibration sense, and positional sense may be reduced or absent and also that ataxia may be present in both conditions. There appear to be no infallible criteria which will distinguish the two lesions except histological examination of the affected structures.

Accordingly, the differential diagnosis during life has to be made on the basis of certain suggestive findings. Thus, hyperaesthesia of calf muscles strongly supports the diagnosis of peripheral neuritis, while loss of vibration sense extending up to the pelvis favours a lesion of the posterior columns. Lastly, a markedly disproportionate increase in the degree of impairment of muscle and joint sensibility and vibration sense on the one hand, as compared with the degree of loss of superficial sensations of touch and pinprick on the other, supports the view that the posterior columns are affected. The presence of an extensor plantar response (positive Babinski sign) clearly indicates that a lesion of the central nervous system is present, but it must be remembered that in pernicious anaemia the lateral columns of the cord are affected much more rarely and usually much later than are the posterior columns. It should also be noted that peripheral neuritis may be due to a specific deficiency of vitamin B₁₂ or it may result from anoxaemia of the peripheral nerves as a consequence of anaemia and cardiac weakness. In the former case it may be present when anaemia is minimal in degree and it will respond dramatically to vitamin B₁₂ therapy. In the latter case it may occur in association with any form of anaemia, but only if the degree of anaemia is sufficiently severe, and it will not respond to vitamin B₁₂ therapy, but will disappear when the haemoglobin level is raised by any method, including blood transfusion.

In assessing the incidence of subacute combined degeneration of the cord in the Edinburgh series of 250 patients, cases have not been included in which the only neurological features were of paraesthesiae and the subjective sensation of unsteadiness, since both these symptoms can be due to causes other than disease of the nervous system. Patients were classified as having involvement of the posterior columns if ataxia was a prominent feature, if tendon reflexes and positional sense were reduced or absent, and if vibration sense was lost as high up as the pelvis. They were classified as having lesions of the pyramidal tract if a spastic gait was present with increased tendon reflexes, extensor plantar response, and a greater or lesser degree of paralysis. These groups are therefore comparable to the two groups described by Cabot (1908) as the "ataxic type" and the "spastic type." Table III shows that involvement of the central nervous system was present in only 11% of Cabot's series and in 7% of the Edinburgh series. This is in contrast to the frequency of occurrence of paraesthesiae as indicated in Table II.

One of the most striking features of Table III is the difference in the degree of anaemia present in the three series when medical advice was first sought. Whereas 21% of Cabot's series had a blood count of less than one million red cells per c.mm., only 1% of the Edinburgh series had a similar degree of anaemia. Panton's series also showed a very high incidence of severely anaemic cases, the average red cell count being 1.39 million per c.mm.

Summary and Conclusions

Evidence is presented to show that the clinical picture of pernicious anaemia is very different to-day from that seen prior to the introduction of liver therapy. This difference is due to the fact that as a consequence of the improved facilities for early diagnosis and treatment which are now available the degree of anaemia in

patients seeking medical advice at the present time is much less than was the case fifty years ago. Hence it is not surprising that certain clinical features which were held to be of particular diagnostic importance in the pre-liver era—namely, jaundice, splenomegaly, acute glossitis, diarrhoea, and subacute combined degeneration of the cord—were present in less than 10% of the patients with pernicious anaemia investigated in the Blood Clinic in Edinburgh during the past ten years. Accordingly, undue emphasis on such features in textbooks of medicine and in lectures is to be deprecated, since it will hinder rather than help early diagnosis.

It is essential to tell undergraduate and postgraduate students that there are no pathognomonic symptoms or signs which will establish the diagnosis of pernicious anaemia; that tiredness, breathlessness, paraesthesiae, and chronic atrophic glossitis are presenting features which occur frequently in other types of anaemia and in particular in cases of iron-deficiency anaemia; and that diagnosis must be based on accurate blood examination, supplemented sometimes by special methods of investigation.

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CLINICAL SIGNIFICANCE OF WEIGHT TRENDS DURING PREGNANCY

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Regular measurement of body weight during pregnancy is clinically valuable. For example, progressive loss of weight helps to confirm the seriousness of vomiting, while a sudden increase of weight may precede the appearance of oedema. It is usually easier to explain a sudden alteration in the rate at which an individual patient gains weight than to explain why overall gains in different patients vary so widely. A few patients gain very little weight, while others gain 50 lb. (22.7 kg.) or more. The impression that many patients who develop pre-eclampsia have high average rates of gain is well substantiated, but there is comparatively little exact numerical information.

The statistical evaluation of weight changes in pregnancy is difficult. A true and complete picture could be obtained only by weighing all pregnant women in a representative community at frequent intervals from conception until delivery, which is practically impossible. It is usual to circumvent the technical difficulties by reporting only on patients fulfilling certain arbitrary criteria. For example, Humphreys (1954) studied 1,000