CLINICAL PATHOLOGY IN GENERAL PRACTICE

LABORATORY INVESTIGATION IN THE HYPERCHROMIC ANAEMIAS

BY

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It cannot be stressed often enough that an anaemic patient should be investigated at least by a blood count and a bone-marrow biopsy before anti-anaemic treatment is started. Unfortunately this is often not done. As a result, the physician is faced later with the almost insuperable problem of trying to decide, for example, whether a patient has or has had pernicious anaemia, when he has already been given active treatment with liver, folic acid, or vitamin B₁₂ without a proper laboratory diagnosis having been made. Since the patient with pernicious anaemia must continue treatment for life, it is of vital importance to be certain of the correct diagnosis in the beginning.

Varieties of Macrocytic Anaemia

Now hyperchromic macrocytic anaemia, although most often seen as pernicious anaemia, may occur in a number of other less common conditions not necessarily related aetiologically to pernicious anaemia. These conditions sometimes cause difficulty in diagnosis, but it is important to make a correct diagnosis, as they often require different types of treatment. Thus, the achylia, or "agastric," macrocytic group comprises primarily the classical pernicious anaemia, but also an identical but much rarer hyperchromic macrocytic anaemia which sometimes follows the removal of the gastric secreting cells by total gastrectomy or the destruction (as by corrosive poisons) of the haemopoietin- and acid-secreting cells of the stomach. If untreated, this anaemia is fatal.

The non-Addisonian group of hyperchromic macrocytic anaemias includes a number of conditions of varying aetiology and treatment. These anaemias are not necessarily progressive and fatal, nor are they usually associated with atrophy of the gastric mucosa or with achylia. They are seen in tropical sprue, idiopathic steatorrhoea (non-tropical sprue), and occasionally in coeliac disease in children; pregnancy; malnutrition; certain diseases of the liver or endocrine disorders; certain neoplastic changes affecting the bone marrow (myelosclerosis); and very occasionally in childhood. There is also a group of idiopathic refractory megaloblastic anaemias.

Patients with a macrocytic anaemia show a variable degree of anaemia, and, according to its severity, there may be a brownish, but more usually a light or pale (lemon) yellowish, colour of the skin and mucous membranes. Those with an achylia anaemia—for example, pernicious anaemia—will frequently have a sore smooth tongue with an atrophic mucous membrane, flatulent dyspepsia, often recurrent mucous diarrhoea, some tingling and numbness in the fingers and toes, and histamine-resistant achylia gastrica. These symptoms are usually quite mild and may be intermittent in the early stages but become persistent and much more severe as the anaemia becomes worse. On the other hand, those with one of the non-Addisonian macrocytic anaemias may show slightly different and often quite diagnostic features. Thus in the anaemias secondary to disturbances of the bowel we find, for example in tropical sprue, that there may be severe malnutrition, loss of weight, glossitis, and typical light-coloured, frequent fatty stools, with changes in fat balance, which may be relieved wholly or in part on return to temperate climates and after a reduced fat intake: usually the gastric secretion

contains both haemopoietin and a more or less normal amount of hydrochloric acid, although sometimes there is achlorhydria gastrica, but it is not necessarily histamine-resistant. In the non-tropical type of sprue, or idiopathic steatorrhoea, similar features are seen usually in adults in temperate climates, but the fatty diarrhoea may be quite mild and vary very much with the dietary fat intake, and it may be necessary to make a fat-balance test to detect this abnormality; the gastric acidity is usually normal, but there may be some decalcification of bones. Coeliac disease, the counterpart of idiopathic steatorrhoea in children, is much more rarely associated with a hyperchromic anaemia; usually there is a hypochromic microcytic or normocytic type of anaemia.

All these sprue-like conditions if associated with a macrocytic anaemia respond to folic acid but not to vitamin B₁₂.

The tropical hyperchromic macrocytic anaemias represent a heterogeneous group probably having several aetiological factors, according to the geographical situation, but in general they are nutritional anaemias probably caused by severe nutritional deficiencies of extrinsic factor and other vitamins and food factors. They often occur in young pregnant women with normal gastric acidity and a normal fat balance, and only rarely are they associated with glossitis and gastro-intestinal symptoms.

There is a definite but relatively uncommon macrocytic or megaloblastic anaemia of pregnancy in which the symptoms and the blood and bone-marrow pictures resemble very closely pernicious anaemia, but the gastric secretion is normal and a therapeutic test shows a rapid remission with folic acid but not following vitamin B₁₂. The patient remains cured and does not require treatment subsequently.

A very uncommon macrocytic (often megaloblastic) anaemia is encountered in children, and has been described as being pernicious anaemia, but it is not a genuine Addison's anaemia; achylia is not necessarily found and the anaemia appears to respond only to folic acid and, poorly, to vitamin B₁₂. Hyperchromic macrocytic anaemia with a megaloblastic marrow and usually normal gastric secretion may be seen in cirrhosis of the liver, and occasionally in diseases of the pituitary and thyroid (hyperthyroidism) glands, severe malnutrition, and neoplastic conditions mainly affecting the marrow as in myelosclerosis.

A typical hyperchromic megaloblastic anaemia without achylia or the Addisonian symptoms of glossitis, flatulent dyspepsia, diarrhoea, paraesthesiae, or neurological symptoms is seen in achrestic anaemia. This is due apparently to inability on the part of the liver to release its anti-pernicious-anaemia "liver principle" when required in the bone marrow.

Occasionally cases of idiopathic refractory megaloblastic anaemia are seen that do not respond properly to any treatment and whose aetiology is unknown. They may have normal or diminished gastric secretion, and often nutritional factors are involved.

Blood Examination

A full examination of the blood will show the following features in pernicious anaemia: a macrocytic hyperchromic anaemia, usually with a much greater reduction in the red-cell count than in the haemoglobin value so that the colour index (although a very inaccurate measure) may be very high (1.3 to 1.6). These changes are paralleled by an

increase in the mean cell volume (M.C.V.) to 95–160 μ^3 (normal 82–95 μ^3), and mean corpuscular haemoglobin (M.C.H.) 33–56 $\gamma\gamma$ (normal 27–31 $\gamma\gamma$); the mean corpuscular haemoglobin concentration (M.C.H.C.) is 32–36% (in iron-deficiency hypochromic anaemia this value is often considerably less than 30%). In the stained blood smear the red cells show marked variety in size (anisocytosis) and bizarre, oval, and pear shapes (poikilocytosis). The cells seem well filled with haemoglobin (mainly owing to their being bigger and thicker in strong contrast with the thin, pale, ring-like cells of hypochromic microcytic anaemia).

In a severe anaemia there will be polychromatophilia, basophilia with fine or coarse basophil stippling, and often some nucleated red cells (normoblasts) may be seen; the last are often noted in haemolytic anaemia. The presence of megaloblasts in the peripheral blood is not common, but is thought to be confirmatory evidence of pernicious anaemia. Sometimes unusual cells such as Howell-Jolly bodies may be seen, but they are not of any diagnostic significance in pernicious anaemia.

The platelets may be diminished in numbers, especially when there is severe anaemia, and may be lower than 50,000 per c.mm.; they increase rapidly with anti-pernicious-anaemia treatment. Clinically, purpuric manifestations, bleeding from the gums, epistaxis, and retinal haemorrhages occur only when severe anaemia is associated with a platelet reduction below about 40,000 per c.mm.

The reticulocytes are usually less than 2% except under two conditions, namely: (a) during spontaneous remissions which are accompanied by a reticulocytosis, and (b) during the first 14 days after adequate anti-anaemic treatment, when a peak of 15–60% occurs at about the sixth to the tenth day, the level being inversely proportional to the initial red-cell count. A persisting irregular reticulocyte count of 5–30% or more suggests a haemolytic anaemia.

Most of the secondary group of macrocytic anaemias described above (sprue, steatorrhoea, pregnancy, etc.) show an almost identical blood picture to that of pernicious anaemia, but, while there are no characteristic differences, tests of the gastric secretions and a therapeutic test allow further differentiation.

Generally the leucocyte count is somewhat reduced (3,000 to 5,000 per c.mm.). Usually there is a relative but sometimes an absolute lymphocytosis (1,000 to 4,000 per c.mm.) due mainly to a reduction of the granular cells. Quite often some large multisegmented (6–10 lobes) polymorphonuclear neutrophilic leucocytes (macropolycytes) are found in the blood smear, and these may appear even before there are gross changes in the red cells; much less frequently a few immature cells, usually myelocytes or metamyelocytes, may be seen.

In passing, it should be mentioned that it used to be common to see a temporary eosinophilia after treatment with liver or liver extracts, but this is a less frequent observation with modern forms of therapy.

Occasionally a patient with a hyperchromic macrocytic anaemia may be found to have a leucocytosis of, say, 10,000–14,000 per c.mm., with 8,000–12,000 being polymorphonuclear leucocytes. This should always suggest either a complicating infection or some other lesion such as a neoplasm of the stomach or lungs for which careful search must be made.

Marrow Biopsy

This has now become an essential procedure in the investigation of any disease of the blood, particularly in early and difficult cases. By its use some of the anaemias previously thought to be refractory have been elucidated and in other blood diseases diagnosis has been established with certainty and at earlier stages.

The technique for obtaining suitable material is simple. The best site in adults is generally the centre of the manubrium sterni, but in children an iliac crest or sometimes a vertebral spine may be easier. The skin is cleaned and infiltrated with a local analgesic, down to and including the periosteum. The sample is obtained with a Salath needle,

gentle suction being applied with a dry 1-ml. "tuberculin" syringe. In children the procedure is much simplified by the use of light anaesthesia, such as with ethyl chloride for two or three minutes, while the iliac crest is punctured at right angles to and just below the upper surface.

Failure to obtain a sample of marrow because of thickened hard bones, or absence of or failure to find a marrow cavity, suggests myelosclerosis.

The specimen obtained, which consists of marrow fragments in a variable amount of blood, is examined after making smears. Some prefer to examine the small fragments of marrow on a slide after they have first been expressed from the syringe on to a watch-glass.

The slide is stained by the Jenner-Giemsa or a similar technique, and examined under the 1/12 oil-immersion lens. An estimate is made of the degree of cellularity, the different types and relative numbers of erythroblasts, granulocytes, lymphocytes, plasma and reticulum cells, and megakaryocytes are ascertained, and any predominating type is noted. In pernicious anaemia and the other hyperchromic (macrocytic) megaloblastic anaemias the marrow picture will be absolutely characteristic. The marrow will be very active (hyperplastic) and contain a high proportion of megaloblasts of all types, sometimes proerythroblasts, often showing various nuclear patterns and active mitosis, but relatively few normoblasts; in milder cases there may be only a few megaloblasts.

In sprue, steatorrhoea, and the tropical macrocytic anaemias quite a number of normoblasts are commonly found, with a transitional rather than a fully megaloblastic type of myelogram; this may be even more marked in coeliac disease in children, who usually show a fully normoblastic marrow.

There is quite often evidence of an unusual and increased leucopoiesis, mainly demonstrated by an increase in the numbers of granular leucocytes and large metamyelocytes; giant hypersegmented polymorphonuclear cells may be noted and probably give rise to the macropolycytes seen in the blood film. On the other hand, there may be a definite reduction in the number of megakaryocytes which parallels the thrombocytopenia in the peripheral blood.

Since this whole marrow picture is typical and pathognomonic for pernicious anaemia and megaloblastic hyperchromic anaemia, it will be realized how important it is to make this examination *before* giving any treatment. The characteristic picture is completely converted to a normoblastic hyperplasia, with disappearance of the megaloblasts, within a few days of giving liver extract, vitamin B₁₂, or folic acid; it thus becomes impossible to make a correct diagnosis afterwards.

In the haemolytic anaemias the marrow shows a very active picture, with plenty of normoblasts of all types (which may be prematurely haemoglobinated), proerythroblasts, and sometimes haemocytoblasts; there are no megaloblasts. Owing to the intense erythroblastic reaction, which may occupy 75% of the cell space, there may be some reduction in megakaryocytes and early granular leucocytes.

Gastric Secretion

Some of the most striking symptoms in the hyperchromic anaemias are referable to the gastro-intestinal tract. Thus the glossitis, flatulent dyspepsia, gastritis, and recurrent mucous diarrhoea are all associated with atrophy of the gastric secretory glands. Every patient with pernicious anaemia (as well as with subacute combined degeneration of the cord) has a complete and irreversible histamine refractory achylia gastrica (commonly a familiar hereditary feature), and normal gastric secretory function is never regained, even after treatment and relief of the gastro-intestinal symptoms.

Whatever may be the other pathological and haematological findings, if free hydrochloric acid is found in the stomach secretion, then the diagnosis cannot be one of pernicious anaemia. On the other hand, the secondary non-Addisonian types of hyperchromic macrocytic anaemias

usually have a normal or slightly reduced gastric acidity, although in patients with tropical sprue, and occasionally in non-tropical steatorrhoea, achlorhydria (not always histamine-refractory) may be noted quite often.

Fat Absorption

While in patients with tropical sprue the typical bulky fatty stools are obvious, it may only be necessary to determine the fat distribution in a simple sample to confirm the gross failure of absorption. In mild cases of sprue and in most cases of non-tropical steatorrhoea and coeliac disease, a single fat analysis may be inconclusive. It is then necessary to carry out a fat-balance test in which the patient is given a fixed diet containing 70 g. of fat, and the fat or fatty acid contents of the faeces are determined daily over a twelve-day test period. The first three daily totals of faeces are bulked together, and the average figure determined for fatty acids. If there is 95% absorption there is no abnormality of fat-splitting and absorption, but less than 70% indicates definite abnormality. If the fatty-acid determination indicates 80-93% fat absorption, further daily estimations must be made until the daily output of fatty acids or fats remains constant. If the value for fatty acids in the daily output is equivalent to less than 90% of the total daily fat intake, the steatorrhoea is confirmed.

Therapeutic Test

When all the preliminary and confirmatory examinations have been made the final test is the therapeutic one.

In pernicious anaemia and the agastric anaemias requiring or expected to respond to hog's stomach, liver extracts, or vitamin B₁₂ (cyanocobalamin), the appropriate dose is given. 1 to 2 ml. of liver extract intramuscularly daily for three days or 100 µg. vitamin B₁₂ subcutaneously daily for two to three days. A reticulocyte count is made daily and determinations of the haemoglobin and the red blood cell count twice weekly. No other treatment should be given during this test. If the diagnosis and treatment are correct then the reticulocyte count will rise rapidly in the course of the following four to eight days to a maximum peak of 15 to 60%, depending on the dosage and potency of the specific treatment and the initial depression of the red-cell count. At an initial level of 1,000,000 red cells per c.mm. a peak of 30 to 40% reticulocytes would be expected, while at 2,000,000 per c.mm. a peak of only 15 to 25% reticulocytes would appear. At the same time the number of red blood cells and the haemoglobin value would rise steadily and progressively to normal levels with further treatment. These results would thus confirm the diagnosis of a macrocytic hyperchromic anaemia due to the expected deficiency.

The non-Addisonian macrocytic hyperchromic anaemias do not respond to liver extracts and vitamin B₁₂. But, after a negative response in the above test, the administration of folic acid, 50 to 100 mg. parenterally for two or three doses, or of 10 to 20 mg. orally daily, will produce a similar haematological response. Failure to respond suggests an error in diagnosis, inadequate or inactive treatment, or some other complicating and concomitant disease or factor.

Conclusion

As a rule the differential diagnosis of these hyperchromic megaloblastic anaemias can be made quite readily by a full blood count, marrow biopsy, and an evaluation of the gastric secretory function.

A diagnosis of pernicious anaemia is certain if there is a macrocytic hyperchromic anaemia, with an active (hyperplastic) megaloblastic bone marrow, and an achylia gastrica, and there is a full haematological and clinical remission after adequate treatment with an active liver extract, vitamin B₁₂ parenterally, or hog's stomach orally. (Note: Folic acid must *not* be given to patients with pernicious anaemia or subacute combined degeneration of the spinal cord, as it causes the onset or worsening of the cord symptoms.) If there is additionally a history of total gastrectomy or

destruction of the gastric mucous membrane, then the pernicious anaemia is secondary to such gastric secretory deficiency.

A hyperchromic macrocytic anaemia with a megaloblastic marrow, but with a normal or reduced gastric acidity, may be seen in sprue, idiopathic steatorrhoea (non-tropical sprue), or coeliac disease. Clinically there may be a history of large bulky frequent pale stools with a variable degree of disturbance of fat absorption as shown by the fat-balance test. This type of anaemia fails to respond to vitamin B₁₂, but improves with folic acid or the less purified types of liver extract. The non-tropical sprue-like conditions may also be associated with a normoblastic marrow, in which case they will not respond to folic acid but will require iron.

A similar hyperchromic anaemia, with megaloblastic marrow, but without achylia gastrica, in a pregnant woman indicates macrocytic or megaloblastic anaemia of pregnancy. This again will respond to folic acid, but not to vitamin B₁₂. It does not require continued treatment.

Next article on Clinical Pathology.—"Investigation of Haemolytic Anaemia," by Dr. John F. Wilkinson.

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RESETTLING MENTAL DEFECTIVES PSYCHOLOGICAL AND SOCIAL ASPECTS*

BY

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The type of adult female defective here discussed is determined primarily by administrative considerations. The ordinary mental deficiency colony caters for all types of defectives and can occupy a considerable proportion of the higher grades in work useful to the institution. A children's hospital such as the Fountain Hospital, which caters for 700 mentally defective children, has no such labour available, as any child who is at all trainable is in the hospital school and occupation centre. For many years, therefore, it was the custom to transfer adult "working" patients from other institutions to the Fountain Hospital to work in the wards and laundry. About 80 such patients were accommodated in the hospital itself, but in 1950 they were transferred to the newly opened annexe, South Side Home, at Streatham.

These patients came from other mental deficiency institutions. It must be stressed that they were classified as unsuitable for licence to a job in the community but possibly suitable for occupation as so-called "workers" in the Fountain Hospital, for which they would receive a small amount of pocket money—formerly sixpence a week but now a few shillings.

Material under Review

Transfers.—From 1918 to the time of writing 327 such adult patients were transferred to the Fountain Hospital. As institutions tend to keep their best workers, those sent to other hospitals are seldom of

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