THE TREATMENT OF THE MACROCYTIC ANAEMIAS

By RONALD H. GIRDWOOD, M.B., CH.B., F.R.C.P.(Ed.), M.R.C.P.(LOND.)

Lecturer in Medicine, University of Edinburgh

Anaemia is said to be macrocytic when the mean corpuscular volume is greater than 95 cu. microns. The macrocytosis may occur in conjunction with a megaloblastic bone marrow, as in pernicious anaemia, a macronormoblastic marrow, as sometimes occurs in chronic hepatic cirrhosis, or a normoblastic marrow as in certain forms of haemolytic anaemia.

Most haematologists in this country use the terminology of Israëls (1939, 1941), or a modification of this terminology, and recognize in truly megaloblastic forms of anaemia three stages after

the proerythroblast in the development of the abnormal red cell precursor. The cells in these stages are frequently referred to as early, intermediate and late megaloblasts, and excellent illustrations of these are available in the textbook by Whitby and Britton (1950).

In addition, however, in certain conditions where megaloblastosis typically occurs, it is not uncommon to find that in some patients the marrow contains not true megaloblasts, but cells with an appearance intermediate between that of the megaloblast and that of the normoblast. There

TABLE I
CLASSIFICATION OF THE MACROCYTIC ANAEMIAS

	Marrow pictures that have been reported in association with macrocytic anaemia		
	Megalo-blastic	Cells intermediate between megaloblasts and normoblasts	Normoblastic or macro-normoblastic
Pernicious anaemia in relapse	+		
Nutritional macrocytic anaemia	+		
Sprue tropical	+	+	+
„ non-tropical	+	+	+
Coeliac disease	+		
Megaloblastic anaemia of infancy	+	+	
'Megaloblastic' anaemia of pregnancy and the puerperium	+		+
Megaloblastic anaemia associated with intestinal strictures, operations and lacteal blockage	+	+	
Diphyllobothrium latum infestation	+	+	
Achrestic anaemia and idiopathic refractory megaloblastic anaemia	+		
Megaloblastic anaemia inadequately treated	+	+	
Leukaemia	+		+
	(rare)		
Haemolytic anaemia	+		+
	(very rare during crisis)		
	(rare)		
Hepatic cirrhosis			+
Multiple myeloma, carcinomatosis and reticulosis			+
After haemorrhage			+
Myxoedema			+
Scurvy			+
Chronic nephritis			+
Aplastic anaemia			+
Osteosclerosis			+
Chronic infections			+

is no satisfactory name for these cells, which have been variously called 'macroblasts,' 'megaloblasts,' and 'intermediate erythroblasts.' Unfortunately, however, Dacie and White (1949) refer to such cells as 'intermediate megaloblasts,' thus using a term that most haematologists reserve for a stage in the development of cells of the true megaloblast series.

Macronormoblastic erythropoiesis differs from the type considered in the last paragraph in that the red cell precursors, although larger than usual, have nuclear structure similar to that of the normoblast. Actual measurements of the size of the marrow cells have been carried out by Dameshek and Schwartz (1940) and by Dacie and White (1949).

It is possible to put forward a classification of the commoner macrocytic anaemias as given in Table 1.

Construction of such a table is difficult owing to the confused state of the literature with regard to bone marrow findings, the fact that many investigators have been content to classify the cells merely as megaloblasts and normoblasts, and the almost complete absence of accurate measurements of the size of the red cell precursors in some of the conditions.

It must be stated, moreover, that although, according to definition, anaemia is not macrocytic if the mean corpuscular volume is less than 95 cu. microns, a normal finding does not necessarily exclude megaloblastic anaemia. Megaloblasts may be found in the marrow, especially in the megaloblastic anaemia of pregnancy, even if the mean corpuscular volume is normal.

Treatment of Megaloblastic Forms of Anaemia

Therapeutic Substances that are Available

In treating patients with megaloblastic anaemia, the practitioner has the choice of using liver extracts, vitamin B₁₂, pteroylglutamic acid (usually referred to as folic acid), hogs' stomach preparations, proteolyzed liver or a combination of some of these substances.

Much progress has been made since Castle and his co-workers, in a series of papers, suggested that the anti-anaemic principle of liver was formed by the interaction of an extrinsic factor in food and an intrinsic factor normally secreted by the stomach. This provided an explanation for the development not only of pernicious anaemia but also of some of the other forms of megaloblastic anaemia. It was found, however, that not all megaloblastic anaemias would respond to liver injections. For this reason the introduction of proteolyzed liver by Davis *et al.* (1943) was an important step forward. Proteolyzed liver, a papain digest of whole liver, was found to

produce a haematological response in forms of megaloblastic anaemia such as 'pernicious anaemia of pregnancy,' which previously had defied all attempts at treatment other than by blood transfusion.

The synthesis of folic acid by Angier *et al.* (1945) made available a therapeutic weapon with great possibilities. Folic acid was found to produce a haematological and clinical response in the initial treatment of all forms of megaloblastic anaemia. Proteolyzed liver had a rather unpleasant taste and varied in haemopoietic potency, but it was now possible to treat even the megaloblastic anaemia of pregnancy successfully with a few milligrammes of folic acid in tablet form. It was found, too, that not only was the megaloblastic anaemia so commonly found in sprue benefited, but that the diarrhoea itself was in many cases improved without, however, any coincidental improvement in fat absorption.

The exact place of folic acid in relation to Castle's theory was difficult to explain, but it was certain that folic acid was neither the extrinsic factor nor the intrinsic factor.

The next development was the simultaneous isolation from liver by Rickes *et al.* (1948) at Merck's Laboratories in the United States and Lester Smith (1948) at Glaxo's laboratories in Great Britain of a highly potent anti-megaloblastic substance which appeared to be the 'specific anti-anaemic factor.' For no very good reason this substance was given the name vitamin B₁₂, and it was isolated in crystalline form both in the United States and in Britain.

Castle and his co-workers (Berk *et al.*, 1948) produced evidence which suggested that not only did vitamin B₁₂ correspond to the anti-anaemic factor but that vitamin B₁₂ or related substances also constituted the 'extrinsic factor.' This is now generally accepted and it is believed that the role of the intrinsic factor is to promote the absorption of vitamin B₁₂ from the alimentary tract in some way as yet not understood. If vitamin B₁₂ is given by mouth to pernicious anaemia patients in amounts therapeutically effective when given parenterally, no haematological response occurs, whereas if normal gastric juice is given simultaneously, there is the expected reticulocyte response and rise in the red cells. This is believed to be because the intrinsic factor in the gastric juice promotes the absorption of vitamin B₁₂. It has been shown (Ternberg and Eakin, 1949) that the intrinsic factor can enter into some form of combination with vitamin B₁₂ *in vitro*, but whether or not this actually occurs in a similar manner in the body is uncertain. Recently it has been shown that liver contains another substance known as folinic acid or the citrovorum factor, which, too, can

effective in the treatment of pernicious anaemia (Davidson and Girdwood, 1951). The name *citrovorum* factor is given because the substance, which is chemically related to folic acid, is necessary for the growth of a streptococcus named *Leuconostoc citrovorum*. This more recently discovered factor, like folic acid, is present only in minute quantities (0.2 to 0.5 µg./ml.) in refined liver extracts, whereas the therapeutically active dose is measured in milligrammes. The therapeutic applications of the discovery of the *citrovorum* factor are still under investigation.

The Interrelationships of the Antimegaloblastic Substances

The metabolic interrelationships of these substances provides a difficult problem which cannot yet be answered. There is, as we have seen, widespread support for the view that vitamin B₁₂, perhaps together with some related forms, is the 'specific anti-anaemic factor.' Whether or not the small quantities of folic acid and folinic acid present in liver extracts can modify the therapeutic activity of vitamin B₁₂ has not been investigated.

The work of Nichol and Welch (1950) and of others suggests that it is likely that folic acid is first transformed to folinic acid in the body before it becomes an effective haematinic agent. If we accept this view, the two main theories at present available to explain the interrelationships of these factors are as follows:—

1. Folic acid is present in the food in a conjugate form which is haemopoietically inactive. After absorption, vitamin B₁₂ releases free folic acid from this conjugate form, thus:—

This theory was originally put forward because it was found that normal persons given the naturally occurring folic acid conjugate could excrete it as folic acid in the urine, whereas pernicious anaemia patients were unable to do so. Subsequent work showed that the interpretation of these findings was complicated by the occurrence of 'conjugase inhibitors' in the natural sources of the folic acid conjugate.

The main support for the theory now comes from the fact that although vitamin B₁₂ is effective only in certain types of megaloblastic anaemia, folic acid is effective in all forms in the initial stages and converts megaloblastic blood formation to the normoblastic type.

The main objection is that pernicious anaemia patients maintained on folic acid frequently show eventual haematological relapse.

2. The second theory, put forward by Vilter *et al.* (1950), is based largely upon bacteriological experiments. This theory suggests that folic acid and presumably folinic acid are coenzymes concerned with the formation of thymine from precursors such as uracil, and that vitamin B₁₂ is concerned with the formation of thymidine from thymine. From thymidine, nucleic acid is derived.

Vitamin B₁₂ might fail to act in folic acid deficiency since the earlier stages of the metabolic process could not take place, and it is suggested that folic acid may be effective in the absence of vitamin B₁₂ by virtue of a 'mass action' effect.

This theory requires further investigation by therapeutic experiment.

In summary, it may be said that, at the moment, the interrelationships between these various haematological factors are uncertain, but that it is likely that vitamin B₁₂, folic acid and folinic acid are all required at some stage for normoblastic blood formation to continue.

Various Forms of Vitamin B₁₂

It has been shown that in addition to vitamin B₁₂ itself, there are the forms vitamin B_{12a} (also known as B_{12a}), B_{12c} and B_{12d}. The chemical formula of B₁₂ itself differs from that of the other forms in that a cyano group is present. All these forms are therapeutically active in pernicious anaemia.

Estimations of the vitamin B₁₂ content of tissues or fluids, including liver extracts, are usually done by microbiological assay methods, and the various forms of vitamin B₁₂ are now believed to differ in the extent to which they support the growth of the test organisms in such assays. If liver extracts are treated with sodium cyanide, however, the apparent vitamin B₁₂ content is often increased, and this is probably due to conversion of other forms to vitamin B₁₂ itself. It is thus possible for different workers to obtain very different results from their microbiological assays of liver extracts according to the technique that they use, and especially depending upon whether or not they first treat the liver extract with cyanide. We cannot, however, state with certainty that cyanide treatment does not free vitamin B₁₂ from forms that are therapeutically inactive, and it is possible that there are modifications or conjugates of vitamin B₁₂ that have not yet been identified.

TABLE 2
APPARENT VITAMIN B₁₂ CONTENT OF VARIOUS LIVER EXTRACTS

Manufacturer	Date of Manufacture	Vitamin B ₁₂ content (L. <i>leichmannii</i> assay)			
		No cyanide added μg./ml.	Cyanide added μg./ml.		
1. Refined Liver Extracts:					
A	1945	5.45	—		
	1946	1.25	—		
	1948	4.0	4.0		
	1949	7.6	—		
	1950-51	9.6	13.8		
	1950-51	10.4	16.7		
	1950-51	8.8	11.4		
	B	1945	2.7	1.7	
		1946	1.4	1.4	
		1947	2.1	2.8	
1947		2.1	4.2		
1947		0.9	0.9		
1948		2.0	—		
1950		3.7	—		
1950		4.8	7.3		
1950-51		5.2	5.2		
1950-51		3.0	5.9		
C	1950-51	5.8	7.0		
	1950-51	5.1	6.2		
	D	1948	0.25	—	
		1949	0.35	—	
		1950-51	4.3	6.5	
		1950-51	6.3	14.3	
		E	1947	1.7	—
			1950-51	8.3	15.1
			1950-51	10.4	16.7
			1950-51	9.7	12.0
F		1950-51	9.3	14.2	
		1948	14.0	—	
	1950-51	7.4	13.8		
G	1950	3.8	3.8		
	1950-51	11.0	24.0		
	2. Crude Liver Extracts:				
A	1948	0.46	—		
E	1950-51	2.5	4.9		
	1950-51	2.4	2.6		
G	1950-51	1.6	2.9		
H	1950-51	1.3	1.8		

Vitamin B₁₂ Content of Liver Extracts

In a previous paper (Girdwood and Carmichael, 1950) there was given the vitamin B₁₂ content of certain British liver extracts that had been manufactured between 1945 and 1950. The work was done before the effects of adding cyanide to liver extracts was known, and hence the estimate made was probably chiefly that of vitamin B₁₂ itself. In most instances the content was low, and although statistical evaluation of the response to therapy in pernicious anaemia is only of limited value, it can be said that there was no evidence from this method of approach to suggest that the therapeutic activity of the liver extracts tested could not be explained on their vitamin B₁₂ content.

More recently, by the kindness of the manufacturers concerned, it has been possible to assay several batches of liver extract produced in 1950 and 1951, and to repeat the assay after treating the extracts with cyanide. Some of the results have already been published (Girdwood, 1951), but in Table 2 the earlier results are compared with the more recent ones and, in addition, it has been found possible to include in a few instances repeats of the earlier assays after the addition of cyanide. It will be seen that cyanide treatment did not make a very great difference to the apparent vitamin B₁₂ content of some extracts, whereas in others the difference was considerable. This is no doubt due in part to variations in man-

facturing technique leading to differences in the forms of vitamin B₁₂ present in the resulting liver extract.

The argument that the therapeutic activity of liver extracts can be explained on their vitamin B₁₂ content is merely strengthened by the new development in assay technique.

The Place of Folic Acid in the Therapy of the Megaloblastic Anaemias

The first great hopes about the future of folic acid in the treatment of the megaloblastic anaemias were dashed when it was found that folic acid would not prevent the neurological complications of pernicious anaemia, and in fact appeared to precipitate them. For this reason the use of folic acid must be restricted to the other forms of megaloblastic anaemia where subacute combined degeneration of the cord is very rarely seen as a complication.

Folic acid does not give rise to neurological disorder in normal persons, or in patients suffering from other forms of anaemia, and there is no evidence that it will produce subacute combined degeneration of the cord if it is given in the usual dosage to pernicious anaemia patients receiving adequate treatment with vitamin B₁₂ or liver extracts. On the other hand, there is no evidence that folic acid has any beneficial effect in such cases, and accordingly there is no point in using it in conjunction with vitamin B₁₂ in pernicious anaemia. In the other forms of megaloblastic anaemia, however, there is a definite place for folic acid therapy.

The reason for the acute onset of neurological complications when pernicious anaemia is treated with folic acid is not obvious. The acuteness of this development in many cases suggests that it is more than a matter of giving something that produces haematological improvement without preventing the natural course of neurological complications. Other suggestions that have been made are that folic acid has a toxic effect on the nervous system in itself (but we have seen that folic acid does not produce neurological complications in normal persons) that an 'imbalance of vitamins' is produced when folic acid is given, or that traces of vitamin B₁₂ remaining in the body may be used up when folic acid produces a haemopoietic response by a 'mass action' effect. Davidson (1947) has suggested that subacute combined degeneration of the cord is normally prevented by some substance other than folic acid that exists in a conjugate form and from which it may be released or made available in some way by vitamin B₁₂.

When folic acid is used therapeutically it is probably best to use tablets of the substance since

folic acid may lose its activity in solution if exposed to light.

The Use of Hogs' Stomach Preparations

The author has had no personal experience of the use of such preparations, which are expensive and less easy for the patient to take, but Wilkinson (1949) reports satisfactory results with this form of therapy in pernicious anaemia. The dose is $\frac{1}{4}$ to 1 oz. daily.

It is possible that such extracts are active when given orally because they contain both intrinsic factor and vitamin B₁₂, the former promoting the absorption of the latter (Bethell *et al.*, 1949).

Bethell, too, working in conjunction with the Upjohn Company of Kalamazoo, Michigan, has prepared extracts of hogs' duodena and vitamin B₁₂ that are active when given by mouth. It is doubtful whether such preparations have any practical advantage since they are no more effective than liver extracts or vitamin B₁₂, and in addition the pernicious anaemia patient may feel tempted to be erratic in taking oral remedies when feeling well. As a result, irreversible neurological complications may develop.

Proteolyzed Liver

The indications for proteolyzed liver preparations are now very limited, since folic acid tablets are so much more convenient to take. According to the information supplied by one of the firms marketing proteolyzed liver, 1 oz. of the preparation (a daily dosage that should be satisfactory for initial treatment) contains approximately 1 mg. of folic acid and 300 µg. of vitamin B₁₂. Although details are not given, the usual method of assay of folic acid is such that it is likely that any folinic acid present is included as folic acid. The therapeutic activity of proteolyzed liver is no doubt due to its content of these substances, although it may be that other unknown factors with an anti-megaloblastic effect are present. Should this be so there may be some place for proteolyzed liver in the treatment of patients with the sprue syndrome who cease to show a haematological response to folic acid.

The Management of a Case of Pernicious Anaemia

It is important to be sure that the patient does, in fact, suffer from pernicious anaemia, and the appearance of blunderbuss forms of therapy for the anaemias, consisting of tablets or capsules containing a mixture of iron, folic acid, hogs' stomach, etc., cannot be too strongly condemned.

For practical purposes the choice lies between the use of vitamin B₁₂ and of refined liver extracts given parenterally. Vitamin B₁₂ has been prepared from various sources, including liver, the

culture fluid of *Streptomyces griseus* and of *Streptomyces aureofaciens*, from a motile bacillus found in hens' faeces, and from horse manure. Satisfactory clinical responses have been obtained from these various preparations.

For the initial treatment, vitamin B₁₂, which now may be obtained in ampoules containing 10, 20, 50 or 100 µg./ml., may be given in a dosage of the order of 50 µg. weekly until the red cell count is normal. The optimal dosage of any liver extract must depend upon its vitamin B₁₂ content, but with a refined extract produced by a reputable firm, 4 ml. given twice in the first week and 4 ml. given weekly until the red cell count is normal, should suffice.

If the anaemia is very severe, the red cell count being one million per cmm. or less, or the patient's general condition precarious, blood transfusion may be necessary. The patient's general condition will depend to a certain extent on the speed with which the blood level is falling. Usually cells from one pint of blood are given *very slowly*. Anaemia may give rise to cardiac failure with raised venous and right auricular pressure, and a further rise in filling pressure on the right side of the heart may lead to a fall in cardiac output. Pulmonary oedema may result.

For this reason, if transfusion is given, the veins in the neck should be examined carefully for evidence of raised venous pressure. Digoxin, which may reduce venous pressure, may be given intravenously.

If subacute combined degeneration of the cord is present it is wise to give large doses of vitamin B₁₂, and 100 µg. to 200 µg. may be administered weekly during the first six months of treatment. If liver injections are given, refined liver extracts should be used, since they contain more vitamin B₁₂. There is no satisfactory evidence that the crude extracts are more beneficial than the refined ones in the treatment of subacute combined degeneration of the cord. Where the neurological features are only those of paraesthesiae, recovery may be guaranteed; where there is evidence of posterior column involvement the chances of complete recovery are good; but where there are signs of lesions of the pyramidal tracts, especially if they are of long duration, the prognosis is very poor. However, there have been numerous reports of a marked improvement following the administration of vitamin B₁₂ or of refined liver extracts even where the plantar responses were dorsiflexor. Re-educative exercises are of great value.

It is not uncommon for iron deficiency to develop during the first few weeks of treatment of pernicious anaemia, and this should be treated with ferrous sulphate, 3 to 6 gr. t.i.d., or ferri and ammonium citrate, 30 gr. t.i.d.

The marrow changes from the megaloblastic to the normoblastic state very rapidly when vitamin B₁₂ or liver extract is given, striking changes being found as early as six hours after the commencement of treatment. On the other hand, reversion to the abnormal state may also be relatively rapid and Mollin and Dacie (1950) have found some reversion to megaloblastic blood formation as soon as 11 days after a small dose of vitamin B₁₂.

The examination of a bone marrow film two or three days after treatment is commenced will, therefore, give definite evidence of a response to therapy. Such a response is often obvious clinically even at this early stage from the improvement in the patient's appetite and sense of well being, and the return of a pink colour to the cheeks. The reticulocyte count in the peripheral blood should be followed, although in other forms of megaloblastic anaemia a reticulocyte response is sometimes seen without a corresponding improvement in the red cell level and, conversely, a very satisfactory red cell rise may be found without the occurrence of the expected reticulocyte peak. Ungley and Campbell (1949), using a vitamin B₁₂ preparation, have given a formula for predicting the expected red cell rise at the 15th day of treatment following single injections of vitamin B₁₂ of varying amounts. If desired, the patient's response may be compared with the predicted response according to the formula of Ungley and Campbell.

Maintenance Therapy

As yet there is little published work on the maintenance therapy of pernicious anaemia patients with vitamin B₁₂. Meacham *et al.* (1950) were unable to maintain the red cells at a satisfactory level with 20 µg. every three weeks, whereas Girdwood (1951) had satisfactory results using 40 µg. every two to three weeks. Vitamin B₁₂ is rapidly excreted in the urine, although it is possible that it circulates in the blood in a 'combined' form (Ross (1951) for several weeks. It seems that a satisfactory dosage for maintenance therapy is 40 to 50 µg. every three weeks. Whether or not 100 µg. every four weeks will be equally satisfactory has not yet been established.

As regards maintenance with refined liver extracts given parenterally, it is not yet quite certain whether or not the activity of such extracts can be explained on their vitamin B₁₂ content alone. This can only be established if satisfactorily controlled tests are carried out using on alternate patients a vitamin B₁₂ preparation and a liver extract of similar vitamin B₁₂ content, and here again we are faced with the difficulty of deciding exactly what is the true vitamin B₁₂ content of a particular liver extract.

The author has not been able to maintain the red cell count consistently at an entirely satisfactory level with 4 ml. of certain refined liver preparations given monthly, although the patients felt well and developed no neurological complications.

Sensitivity to Liver Extracts

Certain patients develop features of sensitivity, such as fever rigors or a rash when injected with liver extracts. Such patients can almost always tolerate injections of vitamin B₁₂ without any difficulty, especially if a crystalline preparation is used. Such preparations are now freely available.

Macrocytic Anaemia in Steatorrhoea

It is uncommon for patients with coeliac disease to have anything other than iron deficiency anaemia, although a megaloblastic form occasionally occurs. In idiopathic steatorrhoea and in tropical sprue, however, a megaloblastic form of anaemia is not uncommon, and sometimes there is found to be a macrocytic anaemia associated with the presence of cells intermediate between megaloblasts and normoblasts, to which we have already referred.

Some sprue patients with megaloblastic anaemia show a response to vitamin B₁₂ whereas others fail to respond to this, but all show an initial haematological improvement when treated with folic acid by mouth or by injection. One possible explanation is that in some instances there is malabsorption of vitamin B₁₂, whereas in other patients the defect is in absorption of folic acid and conjugates. This, however, is not the whole story, since haematological relapse may occur during maintenance treatment with folic acid and because the form of macrocytic anaemia that is not associated with a frankly megaloblastic marrow will not usually respond to folic acid. Whether there is some other haematinic principle missing, whether it is folinic acid, and whether the hypothetical missing substance is present in proteolyzed liver, has not yet been established. Nor do we know why folic acid may sometimes control the diarrhoea without at the same time affecting the percentage absorption of fat.

From the practical point of view, the megaloblastic anaemia associated with steatorrhoea should be treated with folic acid by mouth in a dosage of 10 to 20 mg. daily. At the same time the patient must be treated for steatorrhoea and for other deficiencies in the usual manner. In a severe case, dietetic restrictions may have to be severe, especially in the early stages of treatment, but patients should be encouraged to take as much fat as they can tolerate, since an increase of dietary fat does not reduce the percentage of fat absorbed.

Every patient with the sprue syndrome is an individual problem, and if folic acid therapy alone fails or is not fully efficacious either in the treatment of a macrocytic blood picture or in the control of diarrhoea, then dietetic restrictions may be increased, vitamin B₁₂ may be tried in a dosage of 50 µg. weekly, or liver injections (e.g. 4 ml. of a refined liver extract weekly) may be given. Alternatively, the use of proteolyzed liver merits a trial. There are some patients with steatorrhoea who maintain emphatically that they derive benefit only from one particular brand of liver extract, sometimes a crude extract with a very low vitamin B₁₂ content and negligible content of folic acid and folinic acid. The psychological factor plays a large part in many cases of steatorrhoea, and is responsible for some statements of this nature. Nevertheless a controlled study of the therapeutic value of the different forms of liver extract would be of interest.

Megaloblastic Anaemia of Pregnancy and the Puerperium

For reasons that are not at all obvious, megaloblastic anaemia may occur in pregnancy, or may not be recognized until after delivery. In tropical regions, the condition is probably due in part to primary malnutrition, but Bethell *et al.* (1939), working in the northern parts of the United States, have shown an inverse relationship between the incidence of macrocytic anaemia of pregnancy and the animal protein content of the diet. Goldhamer *et al.* (1939) found that even severe forms of the disorder could be treated by the addition of protein to the diet.

Our clinical impression here is that dietary deficiency is not of primary importance in the pathogenesis of megaloblastic anaemia of pregnancy, and that the condition cannot usually be treated by purely dietetic means. The feeding of 1 lb. or more of liver daily might produce improvement because of the folic acid supplied (probably about 1 to 3 mg. daily), but we have no information about the therapeutic efficiency of folic acid conjugates in the treatment of the condition.

If the anaemia is very severe, blood transfusion should be given slowly. As yet there have been no reports from temperate climates of a satisfactory response to vitamin B₁₂, and no recorded failures with folic acid therapy. Accordingly, folic acid should be given in a dosage of 20 mg. by mouth daily. This dosage may be continued, or reduced after three or four weeks to 10 mg., the administration of folic acid being continued in the puerperium until the red cell level has been normal for a month. Iron therapy will doubtless also be required.

Thereafter the patient should have the blood

checked from time to time for a period of a year, and during subsequent pregnancies. The condition does not necessarily recur.

There is some evidence to suggest that patients who have pernicious anaemia complicated by pregnancy may become temporarily refractory to liver therapy during childbirth (Davidson *et al.*, 1948). If this occurs, folic acid therapy may have to be given as a temporary measure.

Nutritional Macrocytic Anaemia

Whether an aetiological or a morphological classification is adopted, there is no doubt that various forms of nutritional macrocytic anaemia occur. It is possible that there are geographical variations in the types of the disorder, and the matter is made more complex by complicating factors such as pregnancy, dysentery, steatorrhoea, hookworm infestation and malaria. Truly megaloblastic forms of the disease will always respond to folic acid therapy. Sometimes there is a response to vitamin B₁₂ therapy, but as yet there have been no reports of cases that responded to vitamin B₁₂ but not to folic acid.

Since macrocytic anaemia due to primary malnutrition is almost unknown in Britain, the condition will not be considered further, and for the same reason the treatment of megaloblastic anaemia in infancy and the form due to *diphyllobothrium latum* infection will not be considered.

Idiopathic Refractory Megaloblastic Anaemia

The condition of idiopathic refractory megaloblastic anaemia as described by Davis and Davidson (1944) is probably the same as achrestic anaemia as now defined by Wilkinson (1949). These terms were first applied to forms of megaloblastic anaemia for which no cause was obvious and which failed to respond to refined liver extracts. Sometimes free hydrochloric acid was present in the gastric juice. Before such a diagnosis was made it was important to be sure that potent liver extracts were used in treatment, and now vitamin B₁₂ is available to obviate any question of lack of potency of the therapeutic agents employed.

The condition responds to folic acid therapy, and it has been found that some such patients later develop clinical features of the sprue syndrome and that others have evidence of gastric carcinoma.

Treatment of Forms of Macrocytic Anaemia where the Marrow is Not Usually Megaloblastic

Cirrhosis of the Liver

It is generally considered that macrocytic anaemia occurs in hepatic cirrhosis only if the cirrhosis is severe. However, Berman *et al.* (1949)

found no correlation between the severity of the anaemia and the degree of cirrhosis as established by liver biopsy. This may, however, merely be an indication of the inadequacy of liver biopsy methods. The same authors found that of 25 cases, 21 had anaemia and 16 showed macrocytosis. The marrow was macronormoblastic and never megaloblastic.

The occurrence of a true megaloblastic anaemia in association with cirrhosis is probably rare, and some deny its occurrence, but Movitt (1950) has described three cases, one of which was treated successfully with vitamin B₁₂. The commoner macronormoblastic form does not respond to folic acid or vitamin B₁₂.

Renal Disease

Dameshek (1935) and numerous other writers have described hypoplasia of the marrow in chronic renal disease. Recently, however, Cullen and Limarzi (1950) have studied 72 patients with renal disease, 44 of whom had a non-protein nitrogen level of more than 40 mg. per cent. The mean corpuscular volume in these 72 patients varied from 63 to 102 cu. microns, and eight patients had a macrocytic anaemia. The anaemic patients all suffered from azotaemia, but only where the non-protein nitrogen exceeded 150 mg. per cent. was there evidence of hypoplasia.

There is no specific treatment for the anaemia itself.

Scurvy

The anaemia of scurvy is occasionally macrocytic (Vilter and Woolford, 1945), and will respond to the administration of ascorbic acid. If iron deficiency is also present, ferrous sulphate or ferri and ammonium citrate should be given.

Myxoedema

Recently Axelrod and Berman (1951) have investigated the marrow picture in nine patients with myxoedema and have concluded that there is definite hypocellularity of the marrow. They suggest that hypothyroidism should always be considered in any patient having a hypocellular marrow with macrocytic anaemia. Bomford (1938) and others have described a megaloblastic type of anaemia in some cases of myxoedema possibly due to an associated Addisonian pernicious anaemia. In the latter form vitamin B₁₂ therapy will be required in addition to the administration of thyroid extract, but in the usual form of macrocytic anaemia of myxoedema itself, there will be response to thyroid alone.

The Haemolytic Anaemias

A full consideration of the various forms of haemolytic anaemia and of the validity of state-

ments about the size of the red cells in these types would in itself constitute material for an article longer than the present one. Macrocytosis may occur where the reticulocyte count is high, but it may be found even without this.

The types of haemolytic anaemia occurring in this country in which macrocytosis may be found include acute idiopathic haemolytic anaemia (Lederer's anaemia), chronic idiopathic haemolytic anaemia (acquired haemolytic anaemia), and haemolytic anaemic symptomatic of diseases such as chronic lymphatic leukaemia and lymphosarcoma. Sometimes macrocytosis rather than the usual microspheroctytosis occurs in congenital haemolytic icterus.

There is no doubt that splenectomy should be carried out in congenital haemolytic icterus if the anaemia is severe or associated with repeated crises, or if the efficiency of the patient is impaired. If possible this should be done during a remission, careful blood transfusion being given if necessary. It is important that gallstones should be looked for and removed and that a search should be made for spleniculi. Unless crises occur, the spleen should not be removed in children under the age of

ten years. There is no evidence of a beneficial effect of ACTH in the congenital form of the disorder.

In Lederer's anaemia, blood transfusion is usually successful, but sometimes splenectomy is required. In chronic idiopathic haemolytic anaemia, a condition which is probably due to the presence of haemolysins, splenectomy may be successful. Recently there have been reports of remissions which appeared to be the result of ACTH therapy in this condition and in cases of symptomatic haemolytic anaemia (Davidson *et al.* 1951; Dameshek *et al.*, 1951). Further time must elapse before we can assess the true place of this new form of therapy which may prove to be of value in certain instances in preparing patients for splenectomy.

Other Forms of Macrocytic Anaemia

In idiopathic aplastic anaemia and in osteosclerosis, blood transfusion will be necessary. The administration of vitamin B₁₂ and folic acid may be tried although there is unlikely to be a response. In other forms of macrocytic anaemia that have not been considered the treatment is that of the causative condition together with transfusion.

BIBLIOGRAPHY

- ANGIER, R. B., *et al.* (1945), *Science*, **102**, 227.
 AXELROD, A. R., and BERMAN, L. (1951), *Blood*, **6**, 436.
 BERK, L., CASTLE, W. B., WELCH, A. D., HEINLE, R. W., ANKER, R., and EPSTEIN, M. (1948), *New Eng. Journ. Med.*, **239**, 911.
 BERMAN, L., AXELROD, A. R., HORAN, T. N., JACOBSON, S. D., SHARP, E. A., and VONDER HEIDE, E. C. (1949), *Blood*, **4**, 511.
 BETHELL, F. H., GARDINER, S. H., and MACKINNON, F. (1939), *Ann. Int. Med.*, **13**, 91.
 BETHELL, F. H., SWENDSEID, M. E., MEYERS, M. C., NELIGH, R. B., RICHARDS, H. G. (1949), *Univ. Hosp. Bull., Univ. of Michigan*, **15**, 49.
 BOMFORD, R. R. (1938), *Quart. J. Med.*, **7**, 495.
 CULLEN, I. R., and LIMARZI, L. R. (1950), *Am. J. Clin. Path.*, **20**, 3.
 DACIE, J. V., and WHITE, J. C. (1949), *J. Clin. Path.*, **2**, 1.
 DAMESHEK, W. (1935), *Am. J. Med. Sci.*, **190**, 617.
 DAMESHEK, W., ROSENTHAL, C., and SCHWARTZ, L. I. (1951), *New Eng. Journ. Med.*, **244**, 117.
 DAMESHEK, W., and SCHWARTZ, S. O. (1940), *Medicine*, **19**, 231.
 DAVIDSON, L. S. P. (1947), personal communication.
 DAVIDSON, L. S. P., DUTHIE, J. J. R., GIRDWOOD, R. H., and SINCLAIR, R. J. G. (1951), *Brit. Med. J.*, **1**, 657.
 DAVIDSON, L. S. P., and GIRDWOOD, R. H. (1951), *Lancet*, **1**, 722.
 DAVIDSON, L. S. P., GIRDWOOD, R. H., and CLARK, J. R. (1948), *Brit. Med. J.*, **1**, 810.
 DAVIS, L. J., and DAVIDSON, L. S. P. (1944), *Quart. J. Med.*, **13**, 53.
 DAVIS, L. J., DAVIDSON, L. S. P., RIDING, D., and SHAW, G. E. (1943), *Brit. Med. J.*, **1**, 655.
 GIRDWOOD, R. H. (1951), *Edin. Med. J.*, in the press.
 GIRDWOOD, R. H., and CARMICHAEL, K. M. (1950), *Brit. Med. J.*, **11**, 1357.
 GOLDHAMER, S. M., FRITZELL, A. I., and MACKINNON, F. (1939), *J. Clin. Invest.*, **14**, 481.
 ISRAELS, M. C. G. (1939), *J. Path. Bact.*, **49**, 231.
 ISRAELS, M. C. G. (1941), *Lancet*, **11**, 207.
 MEACHAM, G. C., VIGNOS, P. J., HEINLE, R. W., WEISS, BERGER, A. S., and EPSTEIN, M. (1950), *J. Lab. Clin. Med.*, **35**, 713.
 MOLLIN, D. L., and DACIE, J. V. (1950), *Proc. Roy. Soc. Med.*, **43**, 541.
 MOVITT, E. R. (1950), *Blood*, **5**, 468.
 NICHOL, C. A., and WELCH, A. D. (1950), *Proc. Soc. Exptl. Biol. Med.*, **74**, 403.
 RICKES, E. L., BRINK, N. G., KONIUSZY, F. R., WOOD, T. R., and FOLKERS, K. (1948), *Science*, **107**, 396.
 ROSS, G. I. M. (1950), *Nature*, **166**, 270.
 SMITH, E. L. (1948), *Nature*, **161**, 638.
 TERNBERG, J. L., EAKIN, R. E. (1949), *J. Am. Chem. Soc.*, **71**, 3858.
 UNGLEY, C. C., and CAMPBELL, H. (1949), *Brit. Med. J.*, **11**, 1370.
 VILTER, R. W., HERRIGAN, D., MUELLER, J. F., JARROLD, T., VILTER, C. F., HAWKINS, V., and SEAMAN, A. (1950), *Blood*, **5**, 695.
 VILTER, R. W., and WOOLFORD, R. M. (1945), *J. Lab. Clin. Med.*, **30**, 388.
 WHITBY, L., and BRITTON, C. J. C. (1950), 'Disorders of the Blood,' 6th edition, J. and A. Churchill Ltd., London.
 WILKINSON, J. F. (1949), *Lancet*, **1**, 292.