amputated the left leg at the junction of the upper and middle thirds of the tibia on June 5th, 1929. Macroscopic and microscopic examination of the blood vessels at the site of amputation showed nothing special, and the wound healed up well at first. On July 11th, when he was getting about on crutches, slightly varicose veins were noticed in the right leg. In the right foot there was good pulsation in the dorsal artery and in the posterior tibial artery behind the internal malleolus. The brachial systolic blood pressure in both arms was 125 mm. Hg. The "oscillometric index" at the left thigh (above the site of amputation) was three divisions, and that at the right thigh, and also at the right calf, was five divisions.

However, on September 25th amputation through the middle of the left thigh had to be performed because of chronic gangrenous trouble in the stump. Macroscopic examination of the amputated part revealed some periarterial "matting" about the popliteal artery, and microscopic examination showed the artery to contain some not very old thrombus. The patient had apparently, for the last month or so, followed our advice in giving up tobacco smoking altogether. By October 19th the operation wound had almost completely healed, and there were no signs of ischaemic circulation in the stump, but a sequestrum formed, which had to be removed later on. There is still slight discharge from part of the operation wound (February, 1930), though the patient can get about well on crutches.

We confess that in the third case the diagnosis of the exact nature of the condition remains uncertain. The changes in the popliteal artery hardly afforded sufficient explanation, and an ulcer cruris must be very rare indeed as the sole or main symptom of thrombo-angiitis obliterans. The supposition that the large leg ulcer was of the ordinary kind, though without obvious varicose veins, in an individual with very poor local tissue resistance against trauma and pathogenic microbes of low-grade virulence, seemed hardly tenable for the present case. In this connexion we searched especially for any sign, however slight, of congenital haemolytic jaundice (anaemia), but with negative results.*

Remarks.

One of us (F. P. W.) has formerly seen various cases of intermittent claudication of lower extremities in English (non-Hebrew) subjects, some of them medical practitioners, but, so far as he could judge, they were mostly due to arterio-sclerosis (atheroma) of large arteries. He believes that such cases seldom progress to actual gangrene, or die of the disease in question, but in one case a post-mortem examination (after death from another disease) was made by the expressed wish of the patient, and old advanced atheroma of the abdominal aorta and iliac arteries was discovered.† Syphilitic arterial disease is certainly very rarely the cause of symptoms resembling thrombo-angiitis obliterans.‡

Recently, at other London hospitals, Dr. Weber has been given the opportunity of seeing examples of apparently true thrombo-angiitis obliterans in men without any Hebrew ancestry; in one man amputation was necessary, and in another gangrene occurred, followed by death.§ A probably arterio-sclerotic case was that of a doctor who, in 1912, when 49 or 50 years old, suffered from severe ischaemic symptoms in the left leg. Dr. Weber saw him first in 1913. He recovered sufficiently to do very active local work during the war, but developed angina pectoris in 1922. From 1924 he had symptoms of occlusion of various blood vessels. The attacks of angina pectoris continued, and he died with gangrene of the right leg in December, 1926, having refused amputation.

It seems as if intermittent claudication from arterio-sclerosis (atheroma) is almost as much confined to males as is thrombo-angiitis obliterans, and in both classes nicotine is usually a prominent item in the past history. In this connexion one must remember the extreme rarity of nicotine abuse among Jewish women of the poorer classes; but it has even been suggested that the female sex factor bestows constitutional immunity from thrombo-angiitis

obliterans. Cardiac symptoms (slight angina pectoris, etc.) are probably more likely to be associated with intermittent claudication of the lower extremities when the latter is due to arterio-sclerotic changes than when it is due to thrombo-angiitis obliterans. Indeed, in cases of intermittent claudication in lower extremities, due either to arterio-sclerotic changes or to thrombo-angiitis obliterans, the supervention of angina pectoris or coronary artery symptoms (in cases known to Dr. Parkes Weber) suggests that the intermittent claudication is caused by arterio-sclerosis (atheroma)—alone or superadded to thrombo-angiitis obliterans.

PERNICIOUS ANAEMIA AND BLOOD TRANSFUSION.

BY

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THE introduction of liver treatment for pernicious anaemia by Minot and Murphy completely altered the outlook in what was usually a fatal disease. Further research, stimulated by Castle's¹ work, by Sturgis, Isaacs, and Sharp,² and later by Wilkinson³ and by Conner,⁴ has demonstrated the value of hog's stomach in the treatment of this disease. More recently Renshaw⁵ published a case which relapsed on liver and which responded to hog's stomach (ventriculin).

There is a real danger, therefore, that the older methods of treatment may be relegated too much to the background. I have encountered cases that did not respond well to liver treatment, and in many of these the giving of arsenic and a blood transfusion has been largely responsible for tiding the patient over a dangerous period.

The most important point in giving a blood transfusion is correct grouping of the donor. I have sometimes had a little difficulty with Group III serum, as occasionally the clumping is slow and not very definite. In contrast, if clumping occurs in Group II serum, it is usually quick and leaves no room for doubt. It is a wise precaution to confirm all Group IV donors by using also a diagnostic Group IV serum. Brines⁶ recently stated that since adopting this as a routine measure no error in blood grouping has been detected in his laboratory during the past six years. While serious reactions rarely occur with Group IV donors, in my own experience fewer reactions occur when the donor is of the same group as the patient, but, although I prefer patient and donor to be of the same group, I never hesitate to use a Group IV donor, no matter to which group the recipient belongs.

In pernicious anaemia the giving of unsuitable blood is a very serious matter, because, even if the transfusion is stopped at the first sign of restlessness, backache, or dyspnoea, death may follow if the patient is very anaemic. Some time ago I was asked to do a transfusion on a patient with a very low red cell count. As he belonged to Group I—the universal recipient—no care was taken in selecting a donor. After about 40 c.cm. of blood had been given he became restless, and said that the blood was too strong for him. The transfusion was stopped, but the patient died eight hours later. He was grouped again before he died, and was undoubtedly a Group I, unless the particular tubes of serum used were at fault, which is unlikely.

Unmodified blood was used in all the transfusions referred to in this paper, the Louis Jubé syringe being employed. This instrument was demonstrated to me by Dr. Skinner of Sheffield, who described it in the *British Medical Journal*; since then I have done over a hundred transfusions with it, and I regard it as the most convenient method when a transfusion of 500 c.cm. or less is given. Above 500 c.cm. it is sometimes inclined to clot, but fortunately this is noticed early, and the transfusion can be discontinued. Reactions following the use of untreated blood are said by Brines⁶ to be far fewer and less severe than when citrated blood is used.

I wish to record here an unusual reaction which occurred when using a Group IV donor; the patient, who belonged to Group II, was suffering from pernicious anaemia. At

* On the occurrence of chronic leg ulcers in cases of congenital haemolytic jaundice, see F. P. Weber, *Practitioner*, 1920, cxxiv, p. 392; Gänsslen, *Klin. Wochn.*, 1920, ix, p. 1308; *Deut. Arch. f. Klin. Med.*, 1925, cxlvi, p. 22.

† In this case there had likewise been cutaneous xanthoma, and it is referred to at some length by F. Parkes Weber, *Cutaneous Xanthoma*, etc., p. 14, 1924, London: H. K. Lewis and Co.

‡ Cf. A. S. Warthin, *Syphilis of the Medium and Smaller Arteries*, *New York Med. Journ.*, 1922, vol. 115, p. 69.

§ In this case, however, the subsequent microscopical examination (Professor R. Donaldson) revealed atherosclerosis as the arterial disease.

the end of the transfusion the patient's face began to swell, and for ten minutes I was almost afraid to look at him, as the swelling continued. There were no other symptoms or signs; adrenaline, which was given at once, probably prevented more serious complications, such as oedema of the lungs or glottis. It was ten hours before the face was normal, yet at no time did the patient feel backache, dyspnoea, or shivering, while the pulse remained between 70 and 75 per minute.

Some physicians are of the opinion that there is more danger in giving a blood transfusion to a patient with pernicious anaemia than to patients with other forms of anaemia. I have noticed slight reactions quite as often in other types of anaemia; so far from being a dangerous proceeding, blood transfusion is practically devoid of risk if the grouping is correct, and it is often a life-saving measure.

After a transfusion there is frequently an immediate rise of temperature. This rise occurs in spite of using a donor of the same group as the patient, the temperature quickly falling to its usual height or to a lower level. In most cases of pernicious anaemia, when the patient has been running a temperature, there is a decided tendency for it to fall during the succeeding days and for a general improvement to set in, with an increase in the haemoglobin and in the number of red blood corpuscles, but this is not always the case, as will be shown later.

In severe cases of pernicious anaemia, with a low haemoglobin percentage and red blood cell count, it may happen that in spite of liver treatment no improvement takes place or improvement is very slow. This applies to raw liver, cooked liver, and to at least three varieties of liver extracts on the market. This poor response to liver is most noticeable when the patient is very anaemic and has a temperature above 100° F., and where the outlook is unfavourable or at any rate alarming. It is to this type of case that I wish to direct attention, for the results of a timely blood transfusion in these cases may be excellent.

The first three cases, described below, will bring out the points I wish to emphasize.

CASE I.

A woman, aged 49, had been in ill-health for over a year. Three weeks before I saw her she had become very anaemic; examination indicated a typical case of pernicious anaemia. The blood count was as follows: red blood cells 1,250,000 per c.mm.; haemoglobin 30 per cent. The temperature was 100° F.; faintness followed the slightest exertion.

Treatment was started at home, and she was admitted to hospital on the following day. She was given daily half a pound of whole liver, and liver extract equivalent to half a pound of liver; in addition liquor arsenicalis was prescribed for her. The temperature (Chart 1) became higher and higher on each succeeding day. Six days after beginning treatment her condition

CHART 1.

was far worse than on admission. The red blood cells were then 1,000,000 per c.mm., and the haemoglobin 26 per cent. A transfusion of 500 c.cm. of blood was given, and improvement, it will be seen, set in forthwith, the temperature falling. A week after the transfusion the blood count was: red blood cells 1,800,000 per c.mm.; haemoglobin 40 per cent. Two weeks after this the red blood cells were 3,290,000 per c.mm.; haemoglobin 68 per cent.

A more typical and less dramatic case is the following one.

CASE II.

A man, aged 32, was admitted in a more or less desperate condition. A diagnosis of malignant endocarditis was made from the presence of haemic murmurs and a high temperature. The blood count was as follows: red blood cells 830,000 per c.mm.;

haemoglobin 26 per cent.; the average diameter of the red blood cells was 7.8 μ .

He was put on whole liver, half a pound daily, and liquor arsenicalis, but his condition did not improve; during the first five days of liver treatment his temperature became higher (Chart 2). He was delirious at night, and in his lucid moments complained of feeling light-headed. He was given a transfusion of 600 c.cm. of blood, and his temperature then began to fall. His general condition improved, but he was still mildly delirious

CHART 2.

at night. The blood picture was as follows: red blood cells 1,450,000 per c.mm.; haemoglobin 32 per cent.

This condition persisted for a further ten days. At the end of this period he was still running a temperature, which tended to become higher, in spite of the fact that he had had raw liver for fifteen days. A blood count at this stage was as follows: red blood cells 1,500,000 per c.mm.; haemoglobin 33 per cent.

At this point a second blood transfusion was given; after this he began to make good progress, the temperature gradually falling, with distinct improvement in the blood picture. A blood count taken a week later showed the red blood cells to be 3,400,000 per c.mm. He was discharged two weeks later, and was able to get about perfectly well.

CASE III.

A woman, aged 46, was treated with liver for pernicious anaemia, and told to continue taking this in the form of liver extract. For a few weeks she did as she had been advised, but after this apparently she did not take it regularly, until about a year later, when she began to feel weak and noticed that she was again becoming anaemic. When I examined her I was told that she had taken the equivalent of a quarter of a pound of liver daily as extract for the past three weeks. She was mildly delirious at times, but a more alarming sign was persistent dyspnoea. The practitioner who attended her told me that her temperature had kept between 101° and 102.5° F. for several days. The red blood cells were 1,300,000 per c.mm.; haemoglobin 28 per cent.; but from her general condition a fatal issue seemed certain. From that day she received arsenic and half a pound of raw liver daily, and on the next day I gave her a transfusion of 500 c.cm. During the next four days there was a decided tendency for the temperature to fall, and, although this was followed by a rise, the temperature was normal at the end of ten days, and the patient was convalescent in two weeks.

It may be contended that these three patients—and others similarly affected to whom I gave blood transfusions—would have improved on liver alone if left a sufficiently long time, but I was not prepared to run any risks, as I have seen four patients that have died who were given liver and arsenic, and in three of these four blood transfusions had been performed by me. Patients without pyrexia, in whom the red blood cell count was above 1,500,000 per c.mm., were never given blood transfusions, and these slowly but surely improved on whole liver. I do not wish, therefore, to convey the impression that a blood transfusion is essential for all patients with a low red blood cell count, and I admit that even those with a high rise of temperature may possibly weather the storm, but the risk appears to me to be great.

Of the four cases that died, one was the Group I patient referred to above, who died eight hours after the transfusion. Of the remaining three cases, two were given liver extract and no whole liver, as it was thought that they would be unable to take the necessary amount of whole liver, and it was hoped that the extract would be of equal benefit. One of these received a blood transfusion of 600 c.cm., and the other received two transfusions of 500 c.cm. on each occasion. The fourth patient was not given a transfusion, as she was our first case of pernicious anaemia to receive liver, but she vomited repeatedly, and this probably accelerated her death.

I have been told by many that a blood transfusion should not be given to a patient with pernicious anaemia who is running a high temperature, but I have repeatedly given 500 c.cm. of blood to patients with a temperature of 102° F., and so far I have not had a severe reaction either in cases where both donor and recipient were of the same group, or where the donor belonged to Group IV and the patient was of another group.

In most cases of pernicious anaemia, and in all cases where patients have a temperature, I give liquor arsenicalis by the mouth. In three non-febrile cases which were being treated with liver extract, one showed no improvement and the other two only very slow improvement until arsenic was given, when a prompt and rapid increase in the red blood cells took place. In each case a different firm's liver extract was used.

The case of a patient who was kept for thirty-six days on liver extract alone without showing improvement, and who made rapid progress on arsenic, will suffice to emphasize this.

CASE IV.

A man, aged 37, was admitted on November 23rd, 1928. Red blood cells were 1,600,000 per c.mm.; haemoglobin 36 per cent. He was put on liver extract in amounts equivalent to half a pound of whole liver daily without other treatment. The succeeding counts were as follows:

December 4th: Red blood cells 1,620,000 per c.mm.; haemoglobin 37 per cent.

December 15th: Red blood cells 1,650,000 per c.mm.

December 21st: Red blood cells 1,520,000 per c.mm.

December 29th: Red blood cells 1,340,000 per c.mm.

On December 29th liquor arsenicalis was prescribed in increasing doses, and on January 14th the red blood cell count was 3,370,000 per c.mm.

In the concluding paragraph, referring to liver extract, the report⁸ of the Committee on Pernicious Anaemia of the Harvard Medical School states:

"Because one lot of a product has been effective it does not prove that subsequent lots will be satisfactory, as the experience of the committee under the best conditions at one time demonstrated."

Since treating the case just mentioned I have advised patients that, although they may alternate whole liver with liver extracts, on no account must the whole liver be stopped. I always double the dose of extract; if the patient is receiving whole liver in quarter-pound portions, when substituting an extract I prescribe the equivalent to half a pound. This is not a needless precaution, as I have had relapses in patients who said that they had tired of whole liver and had relied entirely on the equivalent amount of liver as extract. It is possible, of course, that these relapses might have occurred even if they had been taking whole liver, but this is doubtful.

The following case will indicate the undoubted superiority of whole liver over liver extract, at any rate in this particular patient.

CASE V.

A man, aged 29, was treated in hospital for pernicious anaemia, and discharged on September 25th, 1929, with a red blood cell count of 3,000,000 per c.mm. He took one and a half pounds of lightly cooked whole liver per week until the beginning of May, 1930, when he tired of liver and began taking liver extract in amounts equivalent to two and a quarter pounds of whole liver per week. During the time he was on whole liver he felt as well as he ever did; in addition to returning to work he was able to play games. From the middle of May, 1930, two weeks after he had substituted liver extract for whole liver, his appetite began to fail, and increasing weakness and anaemia was noticed. At the beginning of June, 1930, he stopped the extract and tried to take whole liver again, but his lack of appetite prevented him from eating much of it during the ensuing week. He was admitted to hospital on June 10th with a temperature of 100.2° F. and a red cell count of 1,040,000 per c.mm.

He was put on whole liver, half a pound a day, and arsenic, without, it must be admitted, very rapid improvement, and two transfusions were given in the course of the next two weeks before the temperature came down and real improvement set in.

Conclusions.

1. Severe cases of pernicious anaemia with a high temperature either do not respond to liver treatment or they respond very slowly.

2. Severe cases with a temperature often respond well to a blood transfusion, and in some cases it is probably a life-saving measure.

3. Improvement takes place quicker if arsenic is prescribed for cases of pernicious anaemia which are under liver treatment.

4. It is safer not to rely entirely on liver extracts. Whole liver should always be included in the diet in every case of pernicious anaemia.

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ACUTE LYMPHOCYTIC LEUKAEMIA.

RECOVERY AFTER INTRAMUSCULAR INJECTIONS OF HOG SPLEEN.

BY

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LYMPHOCYTIC leukaemia is such a rapidly fatal disease that the following account of a recovery may be of interest. In publishing it I wish to point out that I do so merely in the hope of stimulating the interest of others to try the treatment. The suggestion of using spleen extract was put forward on the grounds of the connexion in the etiology and the pathology of the disease and the imperfectly understood functions of the spleen. Workers with more material at their disposal might experiment with further cases and draw their own conclusions from their results.

A girl, aged 8, was brought to the surgery on February 1st, 1930. Her mother complained that she looked pale and tired. On examination no physical signs could be discovered to account for the child's loss of interest and energy, but there appeared to be slight anaemia. She was put on a simple iron mixture, and was seen at intervals of four or five days.

On February 19th her condition appeared to have become suddenly much worse; she was therefore ordered to bed. On the following day the degree of anaemia was found to be much more severe, and a loud systolic murmur was heard over the whole cardiac area, being loudest in the recumbent position. There was visible pulsation of the carotid arteries. The spleen could not be felt, but the liver was enlarged to one inch below the costal margin. The child had had three attacks of epistaxis, and had vomited that morning.

A blood count made on the following day was: haemoglobin 24 per cent.; red cells 1,940,000 per c.mm.; leucocytes 6,100; and colour index 0.63. The differential count was: polymorphonuclear neutrophils 40 per cent.; polymorphonuclear eosinophils 0.5 per cent.; lymphocytes 57.5 per cent.; large mononuclears 1 per cent.; and neutrophil myelocytes 1 per cent. There was great variation in the size and shape of the red cells. Punctate basophilia was prominent, and nucleated red cells were present.

The child continued to get rapidly worse. She was removed to hospital for further investigation, and a blood count made on March 3rd—that is, only twelve days after the first count—showed the following alarming progress of the disease: haemoglobin 12 per cent.; red cells 856,000 per c.mm.; leucocytes 9,600; and colour index 0.7. The differential count now was: polymorphonuclear neutrophils 7.2 per cent.; lymphocytes 87.2 per cent.; and large mononuclears 1.6 per cent. The red cells showed a great deal of change in the form of anisocytosis and poikilocytosis, polychromasia, and punctate basophilia. Normoblasts and megakaryoblasts were now present in percentages of 6.4 and 0.8 respectively. Blood platelets were scanty.

On examination the spleen was found to be still not enlarged, and there was no discoverable enlargement of the lymphatic glands. She was obviously extremely ill, of a pale, yellowish waxy colour, with oedema of ankles and legs; a moderate pyrexia was present. Repeated attempts were made to administer liver extract by the mouth, and a small amount was taken, but it was vomited.

On March 7th the child was too ill to take any notice of anything, and entirely refused food. The next day it was decided to try the intramuscular injection of hog spleen and liver extract alternately. The injections were made into the gluteus medius muscle, and 5 c.cm. of a 40 per cent. albumin-free solution of hog spleen was given. Two days later 1 c.cm. of a 20 per cent. solution