special treatment, disappeared. Small doses of digitalis were given occasionally to stimulate the heart, and to increase the flow of urine. Only at present, after the disappearance of the fever and the ascites, we may make our first attempt to improve the circulation by carefully graduated gymnastics, by massage, and other methods of physical therapeutics. Still, looking back at the time before operation, we may surely say that cardiolysis, though not so successful here as in some other cases, has saved the life of our patient, at least made life bearable to him.

THE SWELLING OF THE LIVER.

Before taking leave of the subject, we have to deal with one of the most striking symptoms of adherent pericardium—namely, the enormous liver. In nearly all cases of adherent pericardium there is a history of swelling of the liver, and many authors mention the fact that the swelling of the liver is beyond all proportion to the general venous stasis. As a matter of fact, we may find, as in our case, the liver a huge hard and painful mass in the abdomen before there is any sign of back pressure in the other veins. Some authors have mentioned the fact without giving an explanation, simply putting the problem before their readers; others have given explanations which cannot be called wholly satisfactory. One may find complete information about this

subject in an excellent little book of Otto Hess.⁶

The following explanation I deduce from the very instructive figures given by Keith in his papers, and from the result of the operation of cardiolysis in our case.

After operation, it struck me that, as I pointed out before, the mechanism of respiration had profited from the cardiolysis much more than the heart

Fig. 9.—Diagram of heart, liver, and diaphragm, and the relation of the crus to these organs.

itself. An objective proof of this improved respiration is given in Fig. 6, II, where the inspiratory heaving of the chest is seen to be much higher than before operation. A second change, not visible in the figure but very conspicuous on inspection of the patient, is brought about by the deep retraction of the operated area during inspiration. Coincident with the improved respiration, the liver became much smaller.

Taking into account the insignificant improvement of the heart's action, it seems probable that a relation exists between the improvement of the respiratory mechanism and the decrease in size of the liver. Keith has shown how the diaphragm in its descent not only compresses the abdominal contents and widens the chest, but actually compresses the liver, so that this particular function of the diaphragm is lost. In adherent pericardium, the wide and flaccid inferior vena cava passes to the heart behind the liver, practically in a groove. Immediately below the diaphragm it receives the contents of the liver veins; immediately above the diaphragm it pours its contents into the right auricle. Behind the vein the crus dextrum, the chief motor of the diaphragm, extends from the lumbar vertebrae to the aponeurosis of the diaphragm, fixing itself to the pericardium under and behind the right auricle (see Keith⁷ and the diagram Fig. 9).

In normal conditions the arrangement of the crura and the border muscles of the diaphragm causes a downward

and forward movement of the central tendon, pericardium heart, and roots of the lungs (Keith), and the liver is pushed in the same direction. All these organs coming down in perfect harmony, the vena cava inferior is gently compressed between the crus and the liver, and by this aid is emptied into the heart. In adherent pericardium, however, the crus and the border muscles of the diaphragm are pulling, but the whole complex of organs is immovably fixed in the chest. The contraction of the crus has not now a gentle action on the vena cava, but compresses it more strongly, the liver remaining in its expiratory position; at the same time the crus pulls on the heart and the pericardium at the spot marked X in Fig. 9. A narrowing or a closing of the vena cava must be the consequence of this movement, the heart not giving way to the traction. So I think in inspiration the issue of the vena cava is narrowed by the traction of the crus, the part of the vena cava behind the liver is compressed by the same movement, and the contents of the vein, not being allowed to flow back, are pumped into the liver veins.

REFERENCES.

- ¹ *Lancet*, 1904, i, pp. 556, 629, and 703. ² Harris, *Indurative Mediastino-Pericarditis*, London, 1895. ³ Brauer, *Arch. f. klin. Chir.*, Bd. 71, Heft 1; and *Verh. des XXI Congresses f. inn. Med.*, 1904. ⁴ G. A. Gibson, *Diseases of the Heart and Aorta*, ed. 1898. ⁵ J. Barr, *BRITISH MEDICAL JOURNAL*, 1906, ii, p. 401. ⁶ *Ueber Stauung und chron. Entzündung in der Leber und den serösen Höhlen*, Marburg, 1902. ⁷ Keith, *Journ. of Anat. and Physiol.*, vol. xxxix, p. 243.

An Address

ON

ANOMALOUS CASES OF PERNICIOUS ANAEMIA.

DELIVERED BEFORE THE PERTHSHIRE BRANCH OF THE BRITISH MEDICAL ASSOCIATION ON NOVEMBER 9TH, 1906.

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GENTLEMEN,—I have been much honoured by your kindness in asking me to come here to-night, and I had some difficulty in thinking of a subject upon which to address you which would be of interest. My experience with the post-graduate classes which have recently been held in Edinburgh has shown me that diseases of the blood are now awakening a very wide interest among men in general practice, and I should like to take the opportunity of talking over with you what I have seen in a large number of cases of pernicious anaemia which have specially impressed me in the last year or two.

I do not propose to discuss the ordinary typical cases, but desire to take up rather those which showed unusual features, either as regards diagnosis, clinical appearances, or the results of treatment.

I have a distinct impression that pernicious anaemia is becoming a more common disease than it was fifteen or twenty years ago. During the last year I have seen 37 cases, 21 in private, 16 in Chalmers Hospital, and in addition a number of cases which were under the care of the physicians in the Royal Infirmary, or were seen in the medical waiting-room, and of which I have not kept full records. A large number of these were, of course, sent to me as being specially interested in the disease, but an almost equal number were met with, so to speak, by chance. A dozen years ago a case of pernicious anaemia was regarded as something of a rarity, even in the Edinburgh Infirmary. Now one would hardly ever see a ward on the medical side without one, and I have on one occasion had as many as six cases at one time in Chalmers Hospital. If this increase in number is a real one, it behoves us to be very much on the look-out for the condition, and to be ready to diagnose it; and this all the more, because it may present itself under the most diverse aspects, and the anaemia may apparently be quite a secondary consideration.

In thinking of the disease, one must keep clearly before one's mind the fact that it is not essentially a blood disease at all, but is a toxæmia of largely unknown, and

possibly very various origin, which affects the blood, the blood-forming organs, the nervous system, and the gastrointestinal tract, in proportions which vary infinitely in different cases. The old idea of pernicious anaemia, that it is a condition of rapidly-advancing anaemia leading within a short time to a fatal issue, must be given up, for cases are on record of very prolonged duration, and there are many in which almost from first to last the anaemia is quite in the background, and the prominent symptoms are those due to the affection of one or other of the other systems mentioned.

I can best illustrate my meaning by describing shortly to you the clinical histories of some aberrant cases.

Amaurosis.

I saw R. S., a man aged 40, last November. He had been rather anaemic in the previous spring, but had rapidly recovered, and for some time before I saw him had had haemoglobin varying from 80 to 100. For three weeks he had been getting blind, and an oculist reported that he had a paracentral scotoma in both eyes without any change in the discs. He had a little difficulty in walking, and his knee-jerks were exaggerated. When I saw him he was a thin man, not specially pale, and with evidence of a little neuritis in both legs and very slightly in both hands. His blindness was so marked that he had to be helped into the room, but there was practically nothing else to be made out about him. When I came to examine his blood I found that the haemoglobin was 80, and the red corpuscles 2,780,000, that is to say, a colour index of 1.4, and, in spite of this relatively high red count, the films were markedly typical of pernicious anaemia. There were many megaloblasts and a great deal of other typical alteration. Of course, here the examination of the blood cleared up the diagnosis at once, which had not been suspected by some other physicians who had seen him. He was put on proper treatment and had begun to mend, when unfortunately he took pneumonia, which carried him off in a couple of days.

Symptoms Resembling Peripheral Neuritis.

Mrs. E., from one of the Colonies, the year before I saw her had complained of numbness and loss of power in her fingers and toes. This gradually progressed until she ceased to be able to walk. She suffered from dropped hand and dropped foot, and as she had in addition very considerable uterine trouble, she got altogether into a very low state of health, but it had never struck any of her attendants to regard her as specially anaemic. When I first saw her I found that she had recovered slightly and was able to walk a little. There was marked wasting of the small muscles of the hands, of the kind that is usual in progressive muscular atrophy. The forearm and upper arm had also wasted slightly, but the shoulder muscles not at all. In the lower limbs there was also wasting and clawing of the feet and wasting of the leg muscles. There was a good deal of impairment of sensation in the areas where wasting had occurred. All the reflexes were lost; Babinski's sign was negative. Here I was misled by the history, and as there was a very considerable amount of uterine and tubal mischief, with a great deal of very foul discharge, considered that the case was one of a toxic neuritis from this source, and possibly from alcohol also, as she had been in a very rough part of the country where medicine could not be procured, and her old nurse had given her large quantities of spirit. At this time, when I first saw her, she did not impress me as anaemic at all, and it did not occur to me to examine the blood.

About a month afterwards I saw her again. During this time the paralytic symptoms had improved, but she had become more anaemic, and when the blood was examined she was found to have red corpuscles 2,160,000, haemoglobin 50, colour index 1.1, while the films were quite sufficiently characteristic. Under treatment her blood improved very greatly, and the paralysis also got much better.

Besides these cases I have seen a number of others which were supposed to be suffering primarily from locomotor ataxy or neuritis and secondarily from anaemia, and the anaemia was put down generally to any cause but the proper one. I do not want to multiply these cases needlessly, but I am anxious to impress upon you that very often the nervous symptoms are prominent before the anaemia comes to be at all marked; and one curious fact about them is that the nervous symptoms and the anaemia very often alternate, the one improving as the other gets worse. On the other hand, in some cases the anaemia may precede the nervous symptoms.

Aphasia.

Last year I saw on several occasions a gentleman who had had a mild attack of pernicious anaemia some months before, but who was holding his own with a red count of about 3,800,000. One day he came to see me, and while we were talking he became aphasic and after a few minutes had a very violent epileptiform convulsion. From this he recovered, but it was repeated a quarter of an hour later while I was taking him in a cab to Chalmers Hospital. He remained there for three weeks, during which time he greatly improved. There

was no recurrence of the fits, nor could any evidence of organic brain disease be made out. Some time after his return home he became more permanently aphasic and mentally enfeebled, and ultimately died in this condition. Unfortunately permission to make a *post-mortem* examination could not be obtained.

Another group of cases are those in which the gastrointestinal symptoms are the most prominent.

Gastro-intestinal Symptoms.

Quite recently I have been attending a lady who, about two years ago, began to suffer from diarrhoea, which had continued practically without intermission until she came under my care, though, of course, it varied in severity. She also came from another part of the world, and it seems that at one time during the course of her illness she was practically comatose for two or three weeks, and at that time she must have been anaemic, as a diagnosis of pernicious anaemia was definitely made after a blood examination. So persistent, however, was the diarrhoea, and so worn out was she by it that a physician specially skilled in tropical diseases regarded the condition as being sprue, and sent her home to this country for treatment. She was also almost paralysed in the lower limbs from either neuritis or possibly a combined sclerosis of the cord. The blood was definitely characteristic, the first count being: Red corpuscles, 2,480,000; haemoglobin, 56; colour index, 1.14. Since I first saw her the red count has fallen to 1,800,000, but is now rising again.

There is, next, a large class of cases in which the stomach symptoms are most prominent; where there is pain, sickness, vomiting, sometimes of blood, and gradual loss of weight. These cases are almost always accompanied by anaemia, and they so closely simulate ulcerating cancer of the stomach without a palpable tumour that I defy any one to make a definite diagnosis without a careful examination of the blood. This is the more necessary because in both these sets of cases a test meal usually shows that hydrochloric acid is absent, which is a condition, of course, associated with gastric cancer. I have over and over again seen cases which I felt certain from the clinical history were pernicious anaemia, and discovered, on examining the blood, that the anaemia was secondary and due to cancer; and, on the other hand, I have seen cases which I thought were cancer and which turned out to be pernicious anaemia.

The diagnosis of the blood is perfectly simple in cancer of the stomach with anaemia; the anaemia is always secondary in type—that is to say, the colour index is low, while in pernicious anaemia of course the colour index is always high, at least in cases of sufficient severity to attract attention by the anaemic appearance.

I have never seen one of those cases which are sometimes referred to in literature, where a gastric cancer alone gave the blood changes of pernicious anaemia, and I think it will be found that most of them date from a time when our conception of pernicious anaemia was not so definite as it is now. There is, of course, no reason why pernicious anaemia should not be associated with cancer in the stomach or anywhere else. I have, as a matter of fact, once seen it associated with cancer of the larynx, which was not recognized clinically, and once with an early cancer of the suprarenal; but in neither of these was there any causal connexion between the two conditions.

Kidney disease also sometimes masks pernicious anaemia, and one case of the kind which I have seen was so unusual that I may quote it rather fully.

Kidney Disease Masking Pernicious Anaemia.

The patient, a woman aged 24, had been anaemic for some time, but the anaemia was quite naturally supposed to be chlorotic. She had had a severe bleeding after the extraction of some teeth in November, 1904, but recovered and was married in the following January. She became pregnant, and was delivered on December 10th of a five and a half months fetus. She had placenta praevia, and lost a great deal of blood at the confinement. She was very pale at this time, and immediately after the confinement the kidneys stopped acting entirely. The catheter was passed repeatedly, but only a drop or two came away. She had a normal temperature, a pulse of 100, of rather high tension, a dry furred tongue, but she was perfectly coherent and conscious. There was no oedema. I saw her three days after this state commenced, when there had been in addition some haemorrhage from the nose, and it is possible that she swallowed some of this blood, as there was melæna afterwards. There was a little subconjunctival haemorrhage in the right eye, a small haemorrhage in the left iris, none in the retina, and no haemorrhages elsewhere. I had been asked to see her because of the kidney mischief. The doctor had been so much impressed by this that he put down the pallor, which was definite enough, entirely to the

kidney condition and to the loss of blood which had occurred at the confinement and which had been considerable, and I do not think that pernicious anaemia had occurred to him at all. There was nothing whatever to attract attention in any of the organs. The uterus was normal, the heart, of course, dilated, with systolic murmurs, but the blood was extremely characteristic: red corpuscles, 1,324,000; haemoglobin, 35; colour index, 1.3; and—what was quite unusual—leucocytes, 31,100. It was quite evident from this count and from the films that one was dealing with a pernicious anaemia, and that the pallor was due to that rather than to the kidney mischief, though that must have been extreme. The leucocytosis, though it was so marked, did not present the characteristics of that due to an inflammatory or septic condition, for the glycogen reaction was a very slight one, and there was, as a matter of fact, no inflammatory condition present except the kidney one. The patient had been treated with all the usual remedies for the uraemic state without any effect, and I suggested that we should try the transfusion of defibrinated blood. This was done on the following day, and she improved slightly; but two or three days afterwards she had a convulsion, followed by others, and died. During the whole week of her final illness she did not pass more than about a tablespoonful of urine, and yet remained quite conscious till near the end.

About the same time I saw another case which was also associated with renal mischief.

Acute Bright's Disease.

The patient (a woman about 50) was sent into Chalmers Hospital suffering from acute Bright's disease. She was pale, oedematous all over, with systolic murmurs in the heart and a very sharp second sound, and the urine was loaded with albumen and contained casts. Under treatment the urine improved to a certain extent, the oedema passed off, but she remained as pale as ever, and on examination of her blood she was found to have very well marked pernicious anaemia, the count being red corpuscles 800,000, haemoglobin 20, colour index 1.25, white corpuscles 23,000. She ultimately died in a more or less uraemic condition, after being about three weeks in hospital. At the *post-mortem* examination, besides the typical changes of pernicious anaemia, the kidneys were found to be extremely contracted, one of them was indeed the smallest contracted kidney I have ever seen, and there was some acute inflammatory mischief in them in addition.

It is interesting to note that in this case also there was a leucocytosis, and in another case which did not otherwise present any special features, I found a leucocytosis of 13,000, and on the strength of it advised the doctor to examine the urine, in which he found a large quantity of albumen.

These are almost the only cases in my whole series in which there has been a marked leucocytosis, and they all had albumen in the urine. I should not like to say from this that the presence of leucocytosis in a pernicious anaemia is conclusive evidence of marked kidney mischief, but it is certainly curious that pneumonia in the course of a pernicious anaemia or as a terminal infection usually does not produce a leucocytosis, but simply a proportional increase of polymorphs, and sometimes not even that; while septic conditions also do not usually affect the leucocyte count. I saw an admirable instance of this quite lately—again a case in Chalmers Hospital.

Intercurrent Pyaemia.

A man had a slight tonsillitis when he was admitted. This passed off, and his pernicious anaemia seemed to be improving. While I was away for my holiday in August he had a rise of temperature, for which no definite cause was found, and which I suspect to have been due to a slight recurrence of the tonsillitis. When I returned, in the beginning of September, I found that his temperature had again risen, that he had a left-sided pleurisy and some effusion of fluid. He died after some days, during which time the leucocyte count did not rise above 4,000, and at the *post-mortem* examination we found fairly numerous abscesses well walled off in such diverse situations as the heart wall, the subcutaneous tissue and muscles in front of the chest, several large abscesses in the kidneys (which, except for the abscesses, were fairly healthy), and one tiny abscess, about the size of a small bean, immediately under the pleura in the left lung. It was from this, of course, that the pleurisy arose. These abscesses could not be explained otherwise than as the result of a pyaemia, and this was probably due to the tonsillar condition, yet no leucocytosis had occurred, and the urine had remained practically normal. A few pus cells had been found microscopically, but there was no albumen.

I have been struck, however, with the frequency with which patients with pernicious anaemia die of what in other cases would be called uraemia. They become gradually more and more drowsy and comatose, often have twitchings, headache, and so on, and in a study of the pathological anatomy of the disease which Dr. Goodall

and I made some time ago, we found that the kidneys were hardly ever quite normal, and were sometimes pretty seriously affected. This may be due, of course, to the fact that a large number of the patients were people pretty well up in years, and very possibly owed their kidney mischief rather to other causes than to their anaemia; but it seems, possible, also, that the toxins which cause the symptoms may, in so far as they are eliminated, be passed out through the kidneys, and may very likely give rise to changes there. In any case, I strongly advise you, if you find a leucocytosis in pernicious anaemia, to think of kidney mischief as a possible explanation of it.

Another set of cases are those in which the symptoms known as nervous prostration are the most prominent. These cases seem to occur principally in women who are past middle life, and are usually of a very chronic type. I have seen cases which went from one doctor to another undergoing Weir Mitchell treatment, electrical applications, and so on, without a diagnosis being arrived at. They are almost always cases of the chronic type, in which the red cells seldom fall below 2,500,000, and as that usually means a haemoglobin percentage of about 70, the anaemia is not marked, and the shortness of breath to which it gives rise is apt to be put down as a neurotic symptom. Sometimes, unfortunately, these cases are difficult to treat, even after the diagnosis is made, but I shall have more to say of that later on.

In yet another series of cases mental symptoms are most prominent. One very striking case which I saw recently began with symptoms like those of peripheral neuritis, and the lady was so depressed mentally as frequently to threaten suicide, and on one occasion to attempt it. Not unnaturally, these manifestations entirely distracted the attention of her doctors from the blood condition, which at that time was not very marked; and I only saw her late in the disease, when the anaemia had become extreme and the case was hopeless. By that time the mental symptoms had almost entirely disappeared.

In another case the mental depression was so marked that the patient was confined in an asylum for some months. While there, she recovered both from her mental symptoms and from the anaemia, and lived without recurrence in a marked way of either of them for about ten years after, although she never was very strong. At the end of this period she had another attack of pernicious anaemia and died.

Of course, delusions and hallucinations are extremely common during the acutely anaemic stage, and I have almost always found that they are apt to take the form of suspicion either of the patient's attendants or of his relatives. I have seen some extremely distressing cases in which patients refused to see or speak to their own husbands or wives because they fancied that they intended some mischief to them. These mental derangements are certainly not due to the anaemia, because they do not necessarily occur when the anaemia is extreme, but are almost certainly to be referred to the general toxic condition.

You will ask me on what one is to ground the diagnosis of pernicious anaemia in cases such as those I have spoken of, where symptoms referable to other systems were more prominent than the anaemia itself? It is from the blood that you must always seek information, and you will require to make a thorough examination of the blood in every suspicious case, because from a film alone the diagnosis cannot always be made with certainty. It is, of course, the easiest thing in the world to diagnose a pernicious anaemia from the film alone when one is dealing with a case in the advanced stage, but in the more chronic conditions and remissions it requires very careful search and expert knowledge to make the diagnosis from films alone.

The essential point in the diagnosis of pernicious anaemia is a high colour index; that is to say, a condition in which the red corpuscles, on the average, carry each more than their proper amount of haemoglobin. This relation must be made out by a very careful estimation of the red corpuscles and of the haemoglobin percentage, and you will find, if you multiply the first two figures of the red count by 2, in order to get the percentage of red corpuscles present, and divide the haemoglobin percentage by the figure so arrived at, that in pernicious anaemia the result will come out as 1, or more usually at some figure between 1.1 and 1.4. On the other hand, cases of secondary

anaemia—as, for instance, from haemorrhage, cancer, sepsis, and so on—invariably show a low colour index—that is to say, something usually well below 1. The average colour index in a well-marked case of chlorosis, for example, is usually about 0.5. In certain pernicious anaemias, especially those extremely rare cases where the bone marrow does not hypertrophy but remains fatty, the colour index may be below 1, and occasionally pernicious anaemias, which have been under treatment and are recovering will show a colour index below 1, usually at about the period when the reds get up to 3,500,000, or thereabouts. This is much more likely to occur if the patient is recovering from a first attack. Later, when the disease has become thoroughly established, the colour index often remains high during the whole period of remission.

There are certain other anaemias, such as the rare leukanaemias, the terminal stages of acute lymphatic leukaemias, and some others even rarer, in which the colour index may rise to 1, or sometimes even above it. But these are hardly likely to come into consideration in the kind of cases we are talking of. If the colour index leaves you in any doubt, the next criterion is the presence of megaloblasts or large nucleated red corpuscles in the film. These appear with constancy in all cases of pernicious anaemia at some time. They are usually more numerous the more anaemic the blood, but they can almost always be found in any case of pernicious anaemia, even during remission, though in the latter set of cases the search may have to be very prolonged and may have to extend over several films.

There are other changes in the blood, such as the presence of granular degeneration in the reds, a leukopenia with a relative lymphocytosis and so on, which are of importance when considered along with other points, but which occur in too many other conditions to be of value alone. Of course, the expression in the film of a high colour index is the presence of a large number of megalocytes, the large red cells which are produced by the loss of the nucleus from megaloblasts, and in using Jenner's stain one finds the polychromatic change in the red corpuscles with infinitely greater frequency in pernicious anaemia in all stages, than in any other disease. This change is shown by the fact that the red corpuscles which suffer from it pick up a certain amount of the basic part of the stain, the methylene blue, in addition to the acid part, the eosin, and thus instead of looking pink in the film, are of various shades of purple; but you will almost always find that the colour index is sufficient to guide you provided that you make an accurate estimation of the reds, and that you use an accurate haemoglobinometer. In my experience the best for clinical work is Haldane's modification of Gowers's instrument.

I have come gradually to be of opinion that pernicious anaemia is seldom, if ever, an acute disease. One comes across cases frequently which die in a few days or weeks from the time when they first come under observation, but if one goes carefully into the history of these cases, one will almost always find that there has been a long period of gradually failing health preceding the fatal attack. The change is usually so gradual that it has perhaps escaped the notice both of the patient and of his medical attendant, if indeed he has been seen by any one. An interesting case of this kind came under my notice within the last few days.

Cases of Long-continued Anaemia: Acute Terminal Attack.

A doctor in a town in the South of Scotland sent me some films from a case with the following history: The patient had just returned from a week's holiday. On the day he left for his holiday he had felt out of sorts and shivery. During the whole time he was away he felt seedy, and developed a pain in his left side. When the doctor saw him he looked very ill, was of the typical lemon-yellow tint, and had a very large spleen—hard and very tender. His temperature was 101° at first, and remained high during the whole course of his illness. The heart was much dilated, and he passed into a state of muttering delirium. The films were absolutely typical of pernicious anaemia in an advanced stage, but there was an unusually high percentage of polymorphs in the leucocytes, and in these a well-marked glycogen reaction.

On going into his history the doctor found that he had been feeling fagged and not up to his work for some months at least, and in all probability the case was one of pernicious anaemia complicated by a terminal septic infection; but as no *post-mortem* examination was obtained it was impossible to find

what relation the enlarged spleen had to this. Of course, it is not unusual to find a certain enlargement of the spleen in pernicious anaemia, but I have never seen it so large and so acutely inflamed as it evidently was in this case.

Another case occurs to me as illustrating this point of long-continued pernicious anaemia with a terminal acute attack. Some years ago I saw an old gentleman with a practitioner in Edinburgh. He had been feeling out of sorts and a little breathless, and the doctor suspected that it might be a pernicious anaemia. I examined the blood, found haemoglobin 75, and red corpuscles 3,100,000, that is to say, a colour index of 1.2. I looked through several films, but could find no megaloblasts, and made a diagnosis of pernicious anaemia on the colour index alone. The patient was put on treatment, and recovered so rapidly that the doctor was a little inclined to be doubtful of the correctness of my diagnosis. I heard nothing of the patient for a year. He had been apparently well in the meantime, and I was then asked to see him again in what would otherwise have been diagnosed as a primary acute attack. The reds had fallen to 1,344,000, with a haemoglobin percentage of 40, and he died a month later with the very low count of 500,000, with 18 per cent. of haemoglobin.

I could cite plenty of other cases to the same effect, but these may suffice. The fact seems to be that an anaemia, provided it comes on sufficiently gradually, and in a patient who is not exposed to any great strain, but who is living quietly, may pass practically unnoticed, and the condition may not be diagnosed until, as is usually the case, it suddenly becomes worse.

EARLY DIAGNOSIS.

This question of early diagnosis is, of course, intimately wrapped up with the matter of treatment, because it is only in cases which are diagnosed reasonably early that treatment is of much value. As of course you all know, pernicious anaemia is a disease in which the symptoms run a cyclic course. You may have an attack with recovery, a period of remission, and one or more recurrences before the end. Now as matters at present stand, we have no means of *curing* pernicious anaemia as we know it in this country. In those cases which are associated with the presence of *Bothriocephalus latus* in the intestine, the expulsion of the dead or decaying worm is followed by a permanent cure provided the anaemia has not advanced too far. It is quite definitely proved to my mind that the toxæmia of most of the pernicious anaemias which one sees in this country is due to some process in the alimentary canal, but I have no sympathy with those who look upon the mouth as the essential source of the condition. I have, it is true, seen many cases of pernicious anaemia with foul mouths and bad teeth. I have, however, seen quite as many in persons with well-kept mouths and teeth, and I have seen the disease in people who for years had not had a tooth in their heads and did not wear plates. I do not believe that the streptococcus or any other organism that we know is responsible for the condition. Everything that one finds in the blood in streptococcus infections is exactly the opposite of what one finds in pernicious anaemia. The anaemia caused by the streptococcus is secondary. It causes a leucocytosis, not a leucopenia, with an excess of polymorphs instead of an absolute diminution as in a pernicious anaemia, and where nucleated red cells appear in the blood, they are normoblasts and not megaloblasts, and this applies equally to acute and chronic infections. The organism of pernicious anaemia—if it is an organism—has still to be found. Over and over again I have examined the faeces of pernicious anaemia patients for ova, parasites, unusual organisms, or anything else, and have been uniformly unsuccessful. The blood of pernicious anaemia represents in some ways a throw-back to the blood of early fetal life, and it seems possible that in the people who become affected there may be an inherent weakness of the resisting power and of the blood-forming organs which allows the bacterial processes which go on in every intestine to get out of hand, so that quite ordinary organisms acquire an unusual virulence, and set up the haemolytic and other toxic processes which one sees in pernicious anaemias. I have been strengthened in this feeling by the fact that within the last few months I have come across three cases of people in middle life whose fathers had died of pernicious anaemia, in one case ten, in another twelve, and in the third eight years before. This seems to point to an inherited weakness of the bone marrow.

TREATMENT.

If there is any reasonableness in this hypothesis, it will

at once be evident what must be the main lines on which treatment should be based. One must bring the patient under the best hygienic conditions possible in order to assist the general resisting powers of the body; one must endeavour to diminish bacterial changes in the intestine, and one must endeavour to stimulate the blood-forming organs.

The first indication is to be met by rest in bed in the first place. This should always be insisted on until the patient is well advanced towards recovery, were it only in order to relieve the dilated heart which is so common; plenty of sunshine and fresh air should be insisted on, and I find that cases do extremely well if they are exposed to the open air as fully as patients suffering from phthisis. Of course, all disturbing influences—excitement, worry, and so on—should be removed, therefore cases do better in hospital or in a nursing home than they do at home, except in exceptional cases.

A very important matter is diet. This must be arranged with care to suit each case, but the broad principles are that as long as the blood count is low, it should consist entirely of milk and farinaceous food; no meat of any kind should be permitted. Of course, this change of diet partly meets the second indication, the diminution of bacterial processes in the intestine. It is not uncommon to find that patients when they are first seen have large quantities of indican and similar substances in the urine, and that after a week or two on a farinaceous diet, these practically disappear. In some cases it may be necessary to supplement this by giving intestinal disinfectants, of which in my experience calomel and salol are the most efficient, and in still others it may be necessary to wash out the bowel daily with large enemata of normal saline solution. Theoretically, the stomach might be washed out as well, but patients who are so seriously ill as to require this are seldom in a condition to stand the strain which it involves. The secretion of hydrochloric acid in the stomach is practically always deficient and usually absent in this disease, and I have sometimes found marked improvement from giving hydrochloric acid and pepsin in several doses after meals.

For the necessary stimulation of the blood-forming organs, arsenic is by far the most useful drug, and my habit is to begin with very small doses, to increase fairly rapidly until the patient just begins to show signs of intolerance, and then to continue with a little more than half the dose which was found to produce this effect. The reason for doing this is that patients vary enormously in their powers of tolerating the drug: some will show symptoms of intolerance with 10 minims of Fowler's solution in the day, others can take 60 with impunity, though this is exceptional. Arsenic has sometimes been given with the view that it was an intestinal disinfectant, but its effect is much more probably due to the fact that it stimulates the bone marrow very vigorously, and it must be remembered that this power of stimulation can be carried too far. It is not wise to keep a patient with pernicious anaemia on arsenic during the whole of his time of remission lest the stimulation be too great, his reserve of marrow hypertrophy be drawn on too soon, and a relapse come on earlier than would otherwise have been the case; for it must be remembered that the progress of the disease is strictly conditioned by the power of the red blood-forming marrow to hypertrophy. If for some reason as yet unknown the marrow does not hypertrophy at all, as happens in the very rare cases of aplastic anaemia, the first attack is always fatal, but from what one sees of cases cut off by intercurrent maladies the process of hypertrophy is in most cases a slow one, and it is only when the normoblastic mode of proliferation of red cells is entirely replaced by the megaloblastic that death necessarily occurs from the anaemia. It must be obvious, therefore, that the marrow should be spared as much as possible, and when once a good result has been obtained by arsenic it should be stopped, and only resumed when an examination of the blood shows that the patient is falling back. This indeed constitutes the principal difficulty in the treatment of these cases. The patient and the doctor are so delighted at the apparent cure of the condition that they neglect to watch the progress of events during the remission, whilst as a matter of fact, it is during the remission that the doctor should be most on his guard, and that the patient should be kept most carefully under observation. In all

these cases the blood should be examined at least once a month, if it is at all possible to do this. If this were systematically done, the lives of pernicious anaemias would be much longer, and there would be much less talk of the necessarily fatal character of the disease.

As regards other drugs than arsenic it must be remembered that iron is an absolute poison in pernicious anaemia. It almost always upsets the digestion, and any one conversant with the pathology of the condition would never give it, because in pernicious anaemia there is always a vast amount of iron stored up in the liver, and this can be drawn upon whenever it is required. If iron is given, it probably increases the store accumulated there, and almost certainly hampers the liver cells in their duty of dealing with toxins. I remember an admirable object lesson of this in one case. A patient with pernicious anaemia had been seen by another consultant, who had advised iron, arsenic, and a meat diet. Under this treatment the man rapidly became worse, and was very nearly at death's door when I saw him. I put him upon the lines which I have already mentioned; he improved almost immediately, recovered a normal blood, and lived a useful life for more than a year before he relapsed.

Iron has sometimes to be given when the blood has become nearly normal, in those comparatively rare cases where the colour index becomes low at this stage, because in all probability the store of iron in the liver is exhausted, but it should be given at no other stage.

I have tried fresh bone marrow, dried bone marrow, and extracts of bone marrow in many different forms, but I have never been able to satisfy myself that they were of the slightest use, and I have often kept cases upon them for some time without any improvement, then changed to arsenic, and found the improvement begin at once. A good many cases have been treated with antistreptococcal serum, and some have recovered, but as almost all of them received arsenic in addition, I do not think that we need look to the serum to cure the disease; and from what I have said it will be evident that any serum given hypodermically might help in promoting general resistance, and that the antibody of the streptococcus has no special value in the treatment.

The most difficult pernicious anaemias to treat are the chronic cases in which the red cells never fall much below 2,000,000. They are most apt to occur in people beyond middle life, and perhaps more frequently in women than in men. One reason for the want of response to treatment may be that they are often associated with arterio-sclerosis or some other general tissue defect. Arsenic is not usually very well borne, and it is not possible to give large doses. One is often driven to rely quite as much on general tonic and hygienic treatment, and even with that the patients are apt to drift into a state of chronic invalidism. Fortunately, however, the danger to life in these cases is comparatively small, and if they will realize their limitations, they can often lead sufficiently happy lives.

Of course, complications must be treated in the usual way, and the nervous symptoms in particular must be watched over very carefully.

The elements of prognosis in pernicious anaemia are extremely difficult to formulate as so much depends not only on the actual condition of the blood but on the general constitution of the patient. Generally speaking, the younger the patient the more likely is a rapid course, but of course there are numerous exceptions to this rule. Just as in all other conditions, obvious constitutional defects, such as alcoholism, syphilis, Bright's disease, and so on, modify the prognosis unfavourably, and it must always be borne in mind that pernicious anaemias have a poor resisting power generally, and are very apt to be cut off by intercurrent maladies, perhaps most frequently of all by pneumonia. It will be obvious, therefore, that it is necessary to shield them from such infections as that of influenza as much as possible. As regards the blood itself as an element in prognosis, it is almost impossible in an acute attack, while the blood is on the downward grade, to make a prognosis from it, though generally speaking a high colour index, the presence of numerous megaloblasts and an excessive leucopenia are unfavourable elements; while a moderate colour index, the absence of megaloblasts in appreciable number, the leucocyte count at or near the normal, and, according

to some authorities, the presence of a fair number of eosinophiles, are favourable signs. With this last point I do not altogether agree, as I have seen numerous eosinophiles shortly before death in a good many cases.

A constantly raised temperature, even though it be comparatively slight in degree, is unfavourable, especially if no definite cause can be found for it.

When a case has got over the first attack, and has begun to improve, one hopes to see the colour index become low, if possible below 1.0, for these cases usually have a long remission. Cases whose colour index remains high are apt to go downhill again rapidly, and on slight cause.

To sum up, then, what I want specially to impress upon you is that pernicious anaemia is by no means an uncommon disease, that many cases are undiagnosed because of the unusual way in which they commence or in which they run their course, and that there is no means of diagnosis except the examination of the blood. If blood examination were made more of a routine matter in ordinary practice, as it might quite well be, we should attain a much greater accuracy in diagnosis, not only of pernicious anaemia but of the most diverse conditions; and if we practise it constantly we shall not only save ourselves many unpleasant surprises, but shall attain a more comfortable certainty about cases which now trouble us unduly.

OBSERVATIONS ON THE POISONED SPINES OF THE WEEVER FISH (*TRACHINUS DRACO*).

By H. MUIR EVANS, M.D.LOND.,
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THE painful wounds inflicted by certain fish which are commonly caught by fishermen around our coasts are well known to all who are in any way brought in contact with the men who supply our markets with fish. However, those who most frequently suffer from the pricks from spinous fishes are trawlers, because the weever is less frequently found in the nets of herring or mackerel fishermen. Amateurs are not infrequently stung through ignorance of the dangerous nature of these fish.

There has been comparatively little written by Englishmen on this subject, and those who would read an interesting account of fish with poison organs will find the whole subject treated historically and descriptively by Dr. Bottard in a book published in 1889 entitled *Les Poissons Vénimeux*.

It is important to bear in mind that the weever fish is not poisonous, although it has a poison organ; that is to say, the fish is perfectly good to eat, and has an excellent flavour, but has the power of inflicting dangerous wounds by certain spines on its dorsal fin, and on either gill cover or operculum.

The following account of the symptoms of a weever sting is quoted by Bottard:

I have been pricked several times by *Trachinus vipera*, and I am able to give an exact account of the various phenomena the result of such an injury.

The symptoms are almost always the same. They differ only according to the depth of the puncture and the site of the wound; also according to the time of the year and the nature of the spine, whether it be dorsal or opercular.

In the month of October, 1885, I was pricked fairly deep in the middle of the palmar aspect of the right thumb. The pain was similar to that of a burn. At the end of only a few seconds all the other fingers, as well as that pricked, had become immovable, and were painfully numb. In two or three minutes the numbness had reached the forearm. The numbness seemed to follow the course of the nerves. The joints were particularly tender. At the end of from five to seven minutes the poison made itself felt on the heart, as shown by somewhat severe palpitation. I then felt cold and shivered. The wounded hand all this time was very painful and tender to the least touch. I was unable to dress it until three-quarters of an hour after the accident, when it was impossible to move the arm, and I was unable to undress myself alone. Three days later the surrounding parts were still very painful, and the tissues were swollen.

Gressin describes the symptoms as follows:

One experiences at first a very acute pain, lancinating and paralyzing, often, among nervous persons, associated with fainting. Then a sort of painful tingling attacks the wounded part, which swells up and becomes inflamed, and if one neglects to attend to it this may go on to phlegmonous inflammation and gangrene. Frequently certain general symptoms, as fever, delirium, and bilious vomiting, accompany

this state. They may last two or three hours, or make themselves felt for several days.

The fishermen attribute, with some reason, this irregularity in the effects to the amount of poison inserted, or to the time of year, the spawning season being the most dangerous.

My investigations into the poison organ of *Trachinus draco* were the result of observing the pain and suffering among all associated with the fish trade, both fishermen and packers. I must express my indebtedness, in the first place, to Mr. Borley, of the Marine Biological Association at Lowestoft, who has examined with me the anatomy, naked eye and microscopic, of the weever, and has also helped me in getting together the literature of the subject; and, in the second place, to Professor Sidney Martin, in whose laboratory and with the help of whose assistant, Dr. Stevenson, the experiments on the physiological properties of the venom took place. I must further thank Dr. Stevenson for the great interest he has taken in the subject and the time he has willingly put at my disposal.

The most recent work on the subject of the venom of *Trachinus draco* is to be found in several communications by M. A. Briot.¹ My own experiments, several years later, were made in complete ignorance of this work, and therefore have the value of being free from any bias. This literature was not referred to in so recent a work as the *Cambridge Natural History* (1905).

The methods adopted by Briot to collect sufficient poison for investigation differed to some extent from those of Phisalix. The latter macerated the gland in chloroform water and glycerine, and the fluid resulting from the maceration was used in his experiments. Briot took the venomous spines and adjacent tissues, pounded them in a mortar, and made a glycerine extract. He employed the filtered liquid for his researches, and used the opercular and dorsal spines of 350 weevers caught between the end of May and the beginning of June and 70 caught in September.

The method that I employed was, I think, more scientific and accurate. I obtained freshly-caught weevers from a buyer who was in the habit of collecting fish for the Board of Trade, and could be thoroughly trusted. These I washed under a tap, and with pledgets of absorbent gauze wiped any mucus and dirt from the opercular spines. I then laid the fish in rows and again wiped the heads with wool. With a sterilized syringe I extracted from within the sheath, by inserting the needle along the groove of the spine, as much poison as possible, obtaining, no doubt, a certain quantity of cellular elements, but I avoided those heads in which there was *post-mortem* staining of the vascular tissue of the sheath. The fluid thus obtained—say, from 100 fish—was collected in a watch-glass and placed in a desiccator (Hempel's), the rim being filled with pure sulphuric acid and the air exhausted by means of a pump. In this way, from nearly 2,000 fish I obtained several grams of dried weever poison. This, before making experiments, was finely powdered in a mortar and dissolved in either distilled water or normal saline solution. These solutions were used either with a certain quantity of solid matter suspended, or filtered, or, better, after being centrifuged, to obtain a clear fluid.

The local effects of the poison injected subcutaneously are described in the passages quoted from Bottard and Gressin. It causes mortification of the tissues, and appears to produce a local paralysis which is very evident in experiments on fish. If the poison be injected in the region of the lateral line, the fish is sharply bent away from the lesion on account of the predominant action of the lateral muscles of the opposite side. These experiments have been repeated in the laboratory of University College, London.

A gold fish (A) 4 in. in length died in one hour and a half after injecting 0.015 gram dried venom.

Another (B) died in four hours with the same dose. Seven minutes after injection it lay on its left side, curved away from the site of inoculation into the muscles of the right lateral line.

Another (C), injected with 0.01 gram, showed the next day some local swelling at the site of injection, and continued to live until ten days after the commencement of experiment. *Post-mortem* examination showed extravasated areas of blood at the site of inoculation, and great congestion of the peritoneum.

Another (D) died three days after injection of 0.01 gram, and showed a marked haemorrhagic area along the track of the needle.

Gold-fish (E), injected with 0.005 gram, died eight days after