and the "smallest" cells, as calculated from the radii of the half-circles shown. The diameters of these cells are given in microns.

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LIVER TREATMENT OF PERNICIOUS ANAEMIA:

ITS EFFECT ON THE POLYNUCLEAR LEUCOCYTE COUNT OF COOKE.

BY

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IN the course of routine blood examinations of the patients of this hospital, consisting of the polynuclear count of Cooke and the Schilling haemogram, it occurred to me to investigate the influence of liver treatment on the polynuclear count in a case of pernicious anaemia which was to undergo that treatment.

The polynuclear count of Cooke is simply a modification of the original Arneth count. The original Arneth count was far too complicated, and as a direct result of this we have two modifications in clinical use at the present day: the polynuclear count described by Cooke and Ponder¹ in 1927, which most closely resembles the Arneth count, and the Schilling haemogram,² which divides the neutrophil leucocytes into those with one lobe to the nucleus, including in this the myelocyte and the metamyelocyte, and those cells with more than one division to the nucleus. In this study we are only concerned with the polynuclear count. This gives a much more delicate picture of the leucocytes than either the Schilling haemogram or a total white count plus an ordinary differential one.³ The Schilling haemogram does not indicate any abnormality in pernicious anaemia apart from an inconstant lymphocytosis.

In the polynuclear count as described by Cooke and Ponder¹ the percentage of leucocytes with one lobe to the nucleus is multiplied by one, the percentage with two lobes by two, and so on up to the percentage with five or more, which is multiplied by five. The numbers obtained added together and divided by 100 give the weighted mean number of lobes of the nucleus per leucocyte. The average number in each group in health is about—

I.	II.	III.	IV.	V.
10	25	47	16	2

This gives a normal weighted mean of 2.75. The average varies slightly from individual to individual and with individual workers. Arneth's mean is normally given as 2.76, and Cooke in 1925⁴ gave his normal as 2.70. My own mean, taken from members of the staff who are healthy, is 2.65. The normal mean can fairly definitely be taken as lying between 2.50 and 2.90. The first two groups of the count (I and II) are spoken of as the left-handed columns, and groups III, IV, and V as the right-handed columns. The numbers in the two groups I and II added together constitute the left hand, and III, IV, and V the right hand. I have divided the right hand by the left hand

and called this the index of right-handedness (R.H.) in tables. Bushnell and Treuholtz⁵ suggested adding together groups I and II and half of group III. This is referred to in the tables as B.T.

Naegeli⁶ described a pronounced hypersegmentation of the neutrophil nucleus in pernicious anaemia. Arneth⁷ in 1920 described the "Rechtsverschiebung" or shift to the right which accompanies the neutropenia characteristic of pernicious anaemia. Cooke⁴ in 1925 showed that in uncomplicated pernicious anaemia there was an increase in the number of cells in groups IV and V and a decrease in groups I and II. In group V are those cells with five or more lobes to the nucleus; in pernicious anaemia we often find cells with seven or eight lobes, and in the case of the macropolycyte⁸ there may be ten to fourteen lobes. This means, of course, that the weighted mean and the index of right-handedness are both high. Jedlička and Béránek⁹ report the neutrophil picture in 36 cases of pernicious anaemia. There is nearly always leucopenia, although there are cases with neutrophil leucocytosis of long duration. These authors found an increase of the number of cells with more than three lobes to the nucleus, but also a shift to the left—that is, a dissociation of the blood picture. They consider this dissociation of the blood picture to the right as well as to the left a characteristic of pernicious anaemia. However, Arneth¹⁰ has subsequently demonstrated that this dissociation to the right and to the left also occurs in lymphatic leukaemia. Jedlička and Béránek point out that this dissociation is most marked at the height of the disease and may disappear during remission. Arneth had previously suggested that the myelocytes observed by some authors are really erythroblasts, so accounting for a certain number of cells in group I. Krjukoff¹¹ describes a similar dissociation in sprue—the appearance of myelocytes together with an increase in the number of hypersegmented forms. This will be referred to later. Whitby¹² describes how in two out of four cases treated with liver the relative lymphocytosis disappeared and the differential count became normal apart from the eosinophilia. He did not describe any changes in the neutrophils. Other writers in the *Lancet* inquiry into the effects of liver treatment¹³ show usually a return to the normal number of leucocytes, but give no detail of the neutrophil picture.

Cooke gives the following numbers of cells per group in his cases of pernicious anaemia. The respective indices are given in the last three columns.

Case.	Group.					Weighted Mean.	B.T.	R.H.
	I.	II.	III.	IV.	V.			
1	11	24	49	15	1	2.71	53.5	1.85
2	6	20	39	22	11	3.08	45.5	2.25
3	6	27	40	22	5	2.93	47.0	2.03
4	7	20	44	24	5	3.00	49.0	2.70
5	7	16	29	39	9	3.27	37.5	3.35
6	12	31	26	23	8	2.78	59.0	1.17
7	20	31	17	16	16	2.77	59.5	0.96
8	16	22	32	16	14	2.90	54.0	1.63
9	10	15	38	24	13	3.05	45.0	3.00
10	6	20	42	20	12	3.12	47.0	2.85

Of these, Cases 7 and 8 both show a dissociation of the count and Case 6 to a lesser degree. Our case before liver treatment showed—

Group I	...	...	...	...	...	1
" II	...	...	...	...	...	16
" III	...	...	...	...	...	39
" IV	...	...	...	...	...	32
" V	...	...	...	...	...	11
Weighted mean	...	...	...	...	...	3.33
B.T.	...	...	...	...	...	36.5
R.H.	...	...	...	...	...	4.58

Possibly Cases 1, 6, and 7 of Cooke's series had some inter-current infection or hidden septic focus causing the low weighted mean.

It occurred to me that possibly liver treatment might bring the large number of cells in groups IV and V down to a normal level as the blood returned to normal, and this is precisely what happened. As the red count rose so the weighted mean and right-handed index fell until they reached what was apparently the normal level for the particular individual, and there they remained constant so long as the liver treatment was continued and for some little time afterwards. The two indices then began to rise again as the number of erythrocytes fell, but not quite so rapidly as had happened at the beginning of the liver treatment. When the second course of liver treatment was begun the two indices fell as the erythrocyte count rose. The accompanying chart gives a clear picture of the result. The index of right-handedness shows much more than the weighted mean the change in the polynuclear count, but is obviously too sensitive to change when the numbers in groups I and II are small.

COMMENT.

In the usual clinical descriptions of pernicious anaemia so much interest is concentrated on the red cells, their haemolysis, size, shape, etc., that the leucocytes have come in for very little attention. It seems, however, that the leucocyte changes may in the end produce more convincing indication towards the elucidation of the etiology of the syndrome than has in the past been thought of. A shift to the right of the Arneth or polynuclear count is not common. It is never found in conditions in which there is any infective process at work. The onset of an infective process swings the count across to the left at once, where it stays until the infection subsides. According to Cooke¹ the shift to the left is not so pronounced as it would be in the case uncomplicated by pernicious anaemia. The conditions in which a shift to the right have been described are pernicious anaemia, sprue, and, according to Arneth,¹⁰ lymphatic leukaemia. Dr. Newham of the London School of Tropical Medicine was kind enough to send me some blood films from two well-established cases of sprue. Both these showed a well-marked shift to the right, with the typical blood picture one has learned to associate with pernicious anaemia. Whether *Bothriocephalus latus* anaemia shows a shift to the left or not I am unable to say.

A recent article by Carbonara¹¹ is extremely interesting, for he found a shift to the right of the Arneth count associated with liver disease. In view of the effect of liver treatment in pernicious anaemia, this work of Carbonara's requires careful investigation and confirmation. If confirmed it certainly would appear to be a link in the chain of evidence. Sprue is looked on by Ashford¹² as a glandular insufficiency on which is superimposed a gastro-intestinal infection with *Monilia psilosis*. However, the more recent work of Lye, Zervas, and Cornwell¹³ has shown that the number of isolations of monilia from stools and gastric contents is no greater in pernicious anaemia than it is in other cases of severe anaemia and gastric achylia. These authors conclude that monilia is unimportant as an etiological factor in either pernicious anaemia or sprue. Elders¹⁷ states that sprue is a deficiency disease, and, after comparing sprue and pernicious anaemia, concludes with the statement that "pernicious anaemia is, like sprue, a deficiency disease, and as such should be curable, or at least amenable to improvement, by well-chosen food." This statement was made at the end of 1924, and how true his words were is seen from the subsequent work of Whipple and the introduction of the

Minot-Murphy diet. On the other hand, Newham, Morris, and Manson-Bahr¹⁸ conclude that pernicious anaemia and sprue are two distinct clinical entities, although having several features in common.

Knott¹⁹ found that after liver treatment in pernicious anaemia there was no diminution in the intensity or the nature of the intestinal infection, that the disappearance of the indirect van den Bergh reaction did not necessarily correspond with a reduction in the intestinal infection, and that cases in which a return to a normal blood picture had occurred might still show just as high a bacterial content of the faeces as when in the acutely anaemic stage. In the face of this conflicting evidence, which tends against the infectious etiology of pernicious anaemia, we are driven back on to the theory propounded by Piney²⁰ that pernicious anaemia can only occur in persons who have a remnant of megaloblastic tissue in the liver—that is, that it is essentially a constitutional disease. This is supported by the frequent familial incidence, and also by the fact that achlorhydria, which is invariably present in pernicious anaemia, also commonly occurs in several members of one family. Naegeli²¹ thinks that there is possibly

some constitutional weakness or abnormality of the bone marrow, due perhaps to the retention of megaloblasts since childhood. He quotes Schaumann as having observed cases of *Bothriocephalus latus* anaemia which recovered, but some of which later suffered from real cryptogenetic pernicious anaemia. This supports the constitutional origin of the syndrome. Haden²² looks on pernicious anaemia as due primarily to an inability of the bone marrow to mature red cells, resulting from the lack of some specific substance, and thus would classify it as a deficiency disease, the deficiency not necessarily

being hepatic. He concludes by saying: "It is more likely due to a failure of absorption, or an elaboration in the intestinal tract of the specific maturing substance, perhaps resulting from a long-existent achlorhydria."

CONCLUSIONS.

1. A case of pernicious anaemia treated with liver showed an abolition of the marked shift to the right of the polynuclear count as the total blood picture returned to normal. When liver treatment ceased the polynuclear count moved over to the right again, to be brought back by more liver treatment.

2. A plea is made for a closer study of the leucocytes by those clinicians who have large numbers of cases of pernicious anaemia to deal with, in the hope that this study may lead to a better understanding of the syndrome than the study of the erythrocytes has done.

3. At the same time it would be of greater scientific interest if all reports of cases of pernicious anaemia contained an account of, in addition to what is called the "typical blood picture" and the achlorhydria, (a) the leucocyte picture, including the polynuclear count or the Arneth count, in addition to Schilling's haemogram; (b) the icterus index; (c) the indirect van den Bergh reaction; (d) the Price-Jones curve. The diagnosis of pernicious anaemia is made much more accurate in the presence of (a) to (d).

My thanks are due to Dr. P. W. Bedford for permission to make use of the clinical material and to Dr. Newham for the blood films from cases of sprue.

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JEJUNAL ULCER ASSOCIATED WITH TESTICULAR PAIN.

BY

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THE following case appears to be worth recording on account of the unusual symptoms.

A man, aged 37, had mumps as a child, but otherwise no illness worthy of note till December, 1915, when he was invalided from the army with dysentery. Shortly after returning to duty he was buried by a shell. He was apparently concussed, and immediately afterwards the thyroid gland was seen to be much enlarged; it gradually became smaller, and now seems to be normal. Shortly after the concussion he began to have attacks of epigastric pain, associated with hunger, about half an hour after meals, and tenderness in the epigastrium to the right of the mid-line. At this time he was having irregular meals and smoked heavily; the pain was relieved by food for about half an hour, and then returned increased, being frequently associated with vomiting. At the beginning the attacks lasted about a week, pain appearing after every meal during this time; there were intervals of two or three months during which he was entirely free from symptoms. The attacks were specially severe during the winter, and were usually accompanied by enlargement of the thyroid gland. They gradually became more frequent and of longer duration.

In July, 1919, he had an attack of unusual severity, and three weeks later, while working in his office, he experienced sudden acute abdominal pain associated with repeated vomiting. An operation was performed for perforated duodenal ulcer, but he was apparently given no instructions as to diet, and he ate what he pleased. He remained well for about two years, after which the symptoms appeared again more acutely, and the pain and tenderness extended across the epigastrium. The stools now showed the presence of occult blood. He was treated for six weeks by dieting, but was not confined to bed. After a short interval the symptoms returned, and in February, 1925, gastro-jejunostomy was performed; following this, he was put on a moderately restricted diet for two months.

Six months later he again had symptoms, but they were not so acute as before the operation; they came on particularly when the weather was cold. The pain became gradually longer in duration, increasing in intensity during the day, independent of meals, and was not now relieved by food. On the other hand, for the first time he started to be wakened by pain between 2 and 3 a.m. This only occurred if he had taken a meal after 7 p.m.

In August, 1926, he first felt a dull aching pain in the testes at the end of the day, when the epigastric pain was most acute. A suspensory bandage gave little, if any, relief. Gradually the pain in the testes became greater, and appeared earlier in the day, together with pain in the loins. He never had these symptoms except when the epigastric pain was present, and there was no abnormality in micturition.

In May, 1928, he was awakened about 3 a.m. by attacks of pain in the testes, so severe as to necessitate injections of morphine. There was general tenderness in the upper abdomen, especially at a point immediately above and to the left of the umbilicus, where a small lump could be felt. It seemed to be fixed to the deeper tissues, and moved with the pulsations of the aorta. Pressure on the lump reproduced the pain in the back and in the testes. The testes themselves were tender, and there was slight hyperalgesia in the loins. The urine was normal, and examination of the urogenital tract revealed no abnormality. An x-ray examination with a barium meal showed a jejunal ulcer in the situation of the tumour. Occult blood was present in the stools. The patient was confined to bed, and treated medically on a strict diet. The pain was rapidly relieved and the tumour gradually disappeared. Since then he has remained on a modified diet, and has become a non-smoker. He has remained free from symptoms, has put on 2 st. in weight, and remarks that he has never felt better in his life.

The two main points of interest in this case are: the association of thyroid enlargement with attacks of epigastric discomfort due to duodenal ulcer, and the pain in the testes and the loins. With regard to this pain, four points may be emphasized. (1) Testicular pain was never

present except when there was pain in the epigastrium. (2) Pressure on the tumour produced pain in the testes. (3) Subsidence of the pain, both in the testes and in the epigastrium, coincided with the disappearance of the tumour. (4) The tumour moved with the pulsations of the aorta, to which it appeared to be fixed. The first three of these points suggest that both testicular and epigastric pain had a common origin.

X-ray examination showed that the jejunal ulcer and the tumour were situated just to the left of the mid-line, at the level of the intervertebral disc between the third and fourth lumbar vertebrae. The sympathetic nerve supply, both of the kidneys and the testes, is derived from the twelfth thoracic and first lumbar segments of the cord. These nerves form a plexus in front of the aorta, and branches from this plexus accompany the renal arteries to the kidneys. Branches from the same plexus accompany the spermatic vessels to the testes, and are also distributed to the ureters. Thus the inflammatory mass associated with the ulcer was situated where the sympathetic plexus, in front of the aorta, would be involved, and the patient's symptoms suggest that pain can be referred to a viscus through sympathetic nerves. The phenomenon also suggests an explanation for the testicular pain in ureteric colic, other than the one advanced by Mackenzie, that both these structures are supplied by branches of the genito-crural nerve.

Periodic stimulation of the sympathetic plexus by the inflammatory mass might be due to periodic vascular engorgement or to actual traction on the plexus. The latter seems the more likely explanation. The traction could be produced by gastric movement, the site of the ulcer being fixed. If this explanation is correct, the coincidence of the epigastric pain with that in the testes suggests that pain due to an ulcer is associated with movement of the diseased viscus, whether the movement be tonic or peristaltic in origin. The persistent character of the pain suggests an alteration in tone as the more likely explanation.

TRAUMATIC FAT NECROSIS OF THE BREAST.

BY

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THE condition of traumatic fat necrosis of the breast was first described in America in 1920 by Lee and Adair,¹ who published two cases. They wrote further on the subject in 1922² and in 1924,³ and since then several cases have been described. The first published in this country was by Keynes.⁴ Later, Hadfield⁵ wrote on the subject.

In these cases, following trauma, there developed in the breast a lump which clinically appeared to be a carcinoma, but on microscopic examination areas of fat necrosis only were found, and no evidence of malignant disease was present. Farr⁶ was able to produce experimentally the characteristic lesions by pinching with forceps the subcutaneous fat of young pigs. Sections of the injured areas showed the typical histological picture of fat necrosis. Farr concluded that in an area of traumatized fat the lipolytic enzyme present in fat and blood is liberated, and acts on the neutral fat, breaking it down into its component parts—fatty acid and glycerol. These substances form the irritant which gives rise to the foreign body reaction producing the lesions of traumatic fat necrosis. Although trauma seems to be the usual factor in the published cases, Gottesman and Zemansky⁷ came across a case in which this cause could be eliminated. Further, they analysed 78 cases of non-malignant breasts, and in 14 found some stage or degree of fat necrosis. They concluded that factors other than trauma may explain the phenomenon, and that the escape of fatty material from a dilated duct and its subsequent decomposition plays a role in the cause of this condition.

Professor M. J. Stewart calls the condition subacute panniculitis. He tells me that in his experience it is not uncommon, and he has met with it in the omentum,