through cardiac insufficiency. When the condition of the heart was improved by digitalis it was able to cope more successfully with the necessities of the situation. In such a case to lower blood pressure is to court disaster.

A case of azotaemic nephritis may terminate through failure of the pump, the tubing, or the filter; in other words, through heart failure, rupture of a vessel as in cerebral haemorrhage, or uraemia.

Uraemia.

What signs and symptoms can rightfully be included under this heading? Personally, I should exclude the diarrhoea and vomiting, which may be regarded as alternative methods of excretion. I have already pointed out that 8 grams of nitrogen can be eliminated by the bowel in this way; and Graham has shown that considerable quantities of ammonium salts are present in the vomit of a uraemic patient. The skin rashes I should also look upon as an attempt to excrete toxins. This leaves us with three groups of symptoms which can be fairly classed as uraemic, but I would urge that these groups are due to different toxic substances and are of different significance.

1. *Convulsions and Amaurosis*.—Though very dramatic symptoms, these are really of less serious significance than the others. Patients may recover not only from the attack, but actually from the nephritis. They may occur also in eclampsia and toxæmic kidney, both conditions from which recovery may be complete. In my series of 160 cases of war nephritis convulsions occurred in 8. They all recovered and escaped without permanent damage to the kidney. It has been suggested that these symptoms are due to some toxin acting on the liver rather than to the kidney lesion. On this view I am in favour of treating such patients with insulin and dextrose, since a hepatic toxæmia is best helped by providing an ample store of glycogen in the liver. But there is no doubt that the best and most rapid relief can be given by prompt venesection. Bennett ingeniously compares the convulsions to tetany, pointing out that there is a reduction of blood calcium in both conditions.

2. *Uraemic Asthma*.—The sufferer from this has been graphically described by Rose Bradford as "a drowsy patient, with hissing respirations and bleeding gums." I believe that the cause of this distressing syndrome is acidæmia from failure of the kidney to excrete acid sodium phosphate. The hydrogen-ion concentration of the blood is consequently raised and the dyspnoea is an attempt at compensation for this by washing out carbon dioxide from the lungs. A compensated alkaline defect may exist without dyspnoea, but an uncompensated alkaline defect will cause dyspnoea and calls for free administration of alkalis. De Wesselow finds that a rise of blood phosphates and a fall in calcium content go together.

3. *Headaches; drowsiness; twitchings; hemiplegia; monoplegia; neuralgias; formication; pruritus*.—All this group of symptoms appear to be associated with nitrogen retention. The actual cause of the symptoms seems to be exudate of lymph and even of actual blood through the capillary wall, especially into the cerebral and the subcutaneous tissues. Small punctiform haemorrhages are commonly seen in necropsies on uraemic patients, and large or small purpuric areas in the skin are not infrequent. Canti considers that a blood urea of 300 mg. is a sure portent of a fatal issue; and I should agree, though I have had one case with a blood urea of 500 mg. reduced to 70 mg. under treatment, and sufficient clinical improvement for the patient to leave hospital. He died, however, about six weeks later. In this case, as there was no dyspnoea, the plan of giving hydrochloric acid was adopted, and the improvement certainly appeared to follow this. It has been suggested that in this way toxic amino-acids are converted into ammonium chloride, but I am not convinced that this is chemically sound. But, as already pointed out, dyspnoea implies an acidæmia calling for free administration of alkalis, under which I have also seen some slight fall in blood urea.

In connexion with nitrogen retention I should like to call attention to the different results given by the hypobromite and urease tests for non-protein nitrogen in the blood. The former method gives the amino-acids as well as the urea, the latter the urea only. Now in health 92 per

cent. of the nitrogen given by the hypobromite test comes from the urea, but it must not be assumed that a similar proportion exists in disease. I have, indeed, found the hypobromite test yield twice as much nitrogen as the urease test in uraemia. In other words, in uraemia there is a large increase in the relative and absolute amount of non-protein nitrogen other than urea, and it is presumably this "unknown" amino-acid fraction which is toxic, since urea is a harmless substance. If only one method is going to be used it is better to employ the hypobromite test. But using both gives most useful information as to the amount of toxic material.

This is well illustrated by the great rise of blood urea, sometimes accompanied by tetany, in cases of pyloric obstruction and in toxic conditions severe enough to produce anuria; here the hypobromite and urease methods may give identical figures showing that the rise of blood urea is merely secondary to failure of excretion; there is not, at any rate at first, any excess of amino-acids produced by altered metabolism. Pyloric obstruction presumably acts by preventing ingestion of fluids into the blood stream, so that there is not sufficient for the kidney to function properly. The combined use of the hypobromite and urease methods is a useful way of recognizing such conditions and of proving that they are not primarily renal in origin.

It will be seen that I do not subscribe to the doctrine sometimes advanced that the symptoms of uraemia are due to one specific toxin, albeit of unknown nature. On the contrary, it seems to me that the three different groups of symptoms above detailed are much more likely to be due to different chemical poisons.

CONCLUSION.

In conclusion, I am conscious that these more recent investigations appear to have had a destructive rather than a constructive effect on treatment. This must be admitted, but new aids to treatment will surely spring from a sounder pathology. In the meantime, our patients will do all the better and be more comfortable if we realize that many of the methods formerly recommended in the treatment of these diseases are impotent where not actually harmful.

FURTHER OBSERVATIONS ON THE MACROPOLYCYTE.

BY

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THE statement that megakaryocytes are not infrequently found in the peripheral blood continues to be repeated in papers and in textbooks, but while not denying that the megakaryocyte may be found in the blood stream, its presence must be extremely rare. I have never seen, in blood films, a cell which faithfully resembled the multinucleated giant cell of the marrow; nor have I seen photomicrographs or drawings of the cells so described that are at all convincing. There is every probability that the vast majority of the so-called megakaryocytes found in blood films belong to one or other class of macropolycyte.

DEFINITION.

The term "macropolycyte" (1927) is applied as a descriptive title to the large or giant polymorphs found in certain conditions. The normal neutrophil polymorphonuclear leucocyte, for brevity called the polymorph, measures 10 to 12 microns in diameter in fixed and stained films. (Plate I and Plate II, Fig. 1.) The title "macropolycyte" is given to the large cells of the polymorph type having a diameter of more than 14 microns. It is of this cell which this paper treats, but for its better appreciation a few details concerning the polymorph may be recounted.

THE POLYMORPH IN HEALTH AND IN INFECTIONS.

The polymorph enters the blood stream from the marrow with a single-lobed nucleus, and as its life in the circulation continues, the nucleus becomes more lobulated until

towards the end of its existence it has four or five segments united by fine strands of chromatin. (Plate I.) In the blood stream, therefore, there are normally cells representing the various periods from youth to senility, and it was found by Arneth (1904) that the numbers of polymorphs with one, two, three, four, or five nuclear segments were remarkably constant in health and could be classified on those lines. My own average normal count—that is, the percentage of cells in the various classes corresponding to nuclear segments—is:

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

This was the average of the counts of 90 normal persons of both sexes between the ages of 12 and 55 years. The greatest possible care was taken to exclude infection at the time the blood was taken, and for two months previously. The teeth, throat, nose, ears, chest, abdomen, and urine were examined, and in many cases radiograms were taken of the chest and teeth.

The length of life of the polymorph in the blood stream has been estimated on experimental and clinical grounds (Ponder, 1926; Cooke and Ponder, 1927) to be approximately three weeks. The figures given above represent a polymorph population comparable to infants, children, men, old men, and senile men, in which the deaths in the older groups are exactly compensated for by the births from the marrow. The figures of the polynuclear count tell us whenever this normal state becomes altered, whether by the addition of an unusually large number of young cells, by the removal of an unusually large number of old cells, by both these conditions combined, or by some interference with the normal development.

It will be noted that no class is provided for cells with more than five nuclear segments. Such polymorphs are so rare in normal blood that when they do occur they are placed in Class V.

In infective conditions the percentage of cells of Classes I and II is increased, and the older cells of Classes IV and V rapidly disappear from the circulation. The count has, therefore, a left-handed drift, as in the following example.

	I.	II.	III.	IV.	V.
Normal	10	25	47	16	2
Typhoid fever	54	31	15	—	—
Scarlet fever	44	43	13	—	—
Measles	45	39	16	—	—
Erysipelas	45	40	14	1	—
Diphtheria	41	39	17	3	—
Rubella	30	35	32	3	—
Varicella	33	35	28	4	—
Pertussis	34	39	27	—	—
Puerperal sepsis	42	37	21	—	—
Cerebro-spinal fever	40	45	14	1	—
Lobar pneumonia	57	26	15	2	—

These facts make the appearance of the macropolycyte the more remarkable, because, although a fairly rare cell,

it is found in infections associated with a polymorphic leucocytosis and a left-handed polynuclear count.

THE MACROPOLYCYTE.

On morphological grounds macropolycytes may be divided into two classes. The first, or Type I, macropolycyte resembles the other polymorphs of the blood film in that its nuclear structure and fine oxyphil granules are indistinguishable from those in the polymorph, but differs from that cell by reason of its large size and by the hypersegmentation of its nucleus.

The second, or Type II, macropolycyte may be styled "the megakaryocyte type," because its gnarled nucleus and

PLATE I.

The five classes of the Arneth or polynuclear count. If there is any band of nuclear tissue, except a chromatin filament, uniting the nuclear masses, those parts must not be considered as separate segments. Class I, No. 2, Class II, Nos. 3 and 4, Class III, No. 4, and Class IV, No. 5, illustrate this point. In Class V, No. 4, the upper segment of the nucleus overlies the segment below it, but the thin chromatin filament uniting them can be seen on the left.

coarse granules, some of which are azurophil in staining reaction, resemble to some extent those of the bone marrow giant cell. The conditions in which these giant polymorphs are found are:

I. *The Type I Macropolycyte*.—(1) In health. (2) In infections and in other states in which there is bone marrow reaction—for example, the acute pyogenic infections, acute tuberculosis, certain cases of carcinoma, the exanthemata, myeloid leukaemia, malaria,* and in rabbits with experimental anaemias due to ricin and repeated haemorrhages. (3) In Addison's anaemia.

II. *The Type II macropolycyte*, or the megakaryocyte type, is, so far as my own experience extends, found only in cases of Addison's anaemia in grave relapses.

Before proceeding to further discussion of the two types, the moment is opportune to suggest that, although the Type I macropolycyte found in Addison's anaemia may be morphologically identical with its prototype found in health and in intoxications, the cause of its appearance is probably very different. For this reason the Type I macropolycyte

* The fact that macropolycytes occurred not infrequently in malaria was pointed out to me by Dr. D. U. Owen, clinical pathologist, Liverpool School of Tropical Medicine.

of health and of intoxications would be better considered together, and both the types found in Addison's anaemia classed under the heading "the macropolycytes of Addison's anaemia."

The Type I Macropolycyte in Health and in Conditions of Abnormal Marrow Activity.

1. *In Health.*—Macropolycytes are extremely rare in health, no example being seen in the blood films of the 90 investigated normal persons that formed the basis of our average normal count. Recently, however, I observed a macropolycyte in a man, aged 34 years, whose polynuclear

PLATE II.

FIG. 1.—A normal polymorph. ($\times 1,000$ diameters.)

FIG. 2.—Macropolycyte, Type I, from a case of staphylococcal osteomyelitis. ($\times 1,000$ diameters.)

FIG. 3.—Macropolycyte, Type I, from a case of streptococcal septicaemia. ($\times 1,000$ diameters.)

FIGS. 4 AND 5.—Macropolycytes, Type I, from a case of mixed infection by *Staphylococcus aureus* and *Bacillus coli*. ($\times 1,000$ diameters.)

FIG. 6.—Macropolycyte, Type I, from a case of streptococcal endocarditis. ($\times 1,000$ diameters.)

FIG. 7.—Macropolycyte, Type I, from a case of carcinoma of the breast. ($\times 1,000$ diameters.)

count had previously been included in the original 90. He was reinvestigated, but no focus of infection could be found. The counts of the two occasions were almost identical:

I.	II.	III.	IV.	V.
11	31	42	14	2

The count has a weighted mean of 2.65, which falls close to the average normal mean of 2.74, and within the limits of normality. I think we must accept the fact that macropolycytes do very occasionally appear in normal blood films.

2. *In Conditions of Abnormal Marrow Activity.* This type is illustrated by the Figs. 2 to 7 in Plate II.

Plate II, Fig. 2 is a macropolycyte found in a case of staphylococcal osteomyelitis, which had the following blood count:

Total leucocytes	...	...	...	18,000 per c.mm.
Polymorphs	...	...	...	87 per cent.
Polynuclear count	...	...	...	41; 43; 15; 1; 0.

Plate II, Fig. 3 is a macropolycyte from a case of streptococcal septicaemia.

Total leucocytes	...	...	...	26,000 per c.mm.
Polymorphs	...	...	...	79 per cent.
Polynuclear count	...	...	...	34; 43; 21; 2; 0.

Plate II, Figs. 4 and 5 are macropolycytes from a case of a mixed infection by *Staphylococcus aureus* and *Bacillus coli*.

Total leucocytes	...	...	...	23,700 per c.mm.
Polymorphs	...	...	...	88 per cent.
Polynuclear count	...	...	...	45; 39; 15; 1; 0.

Plate II, Fig. 6 shows a macropolycyte from a case of streptococcal endocarditis.

Total leucocytes	...	...	...	16,000 per c.mm.
Polymorphs	...	...	...	76 per cent.
Polynuclear count	...	...	...	39; 34; 26; 0; 0.

Plate II, Fig. 7 is a macropolycyte from a case of carcinoma of the breast.

Total leucocytes	...	...	...	14,500 per c.mm.
Polymorphs	...	...	...	76 per cent.
Polynuclear count	...	...	...	35; 37; 26; 2; 0.

It will be seen that the macropolycytes have hyper-segmented nuclei, although polymorphs with single and bilobed nuclei predominate in the blood films. What is the explanation of their presence? It is not easy nor particularly important to determine why macropolycytes appear in health and in infections, because they are rare and do not seem to have any prognostic or diagnostic significance. There are two possible explanations of their presence. The first, that they may represent an occasional polymorph that has escaped the physiological mechanism whose function is the destruction of aged leucocytes and their removal from the blood stream. A polymorph has been imprisoned in some tissue space, exceeded its allotted span of life, and continued to develop beyond the normal limits. The result is that it has become a giant. The second explanation is that they are cells whose development has been altered by an abnormal medium to which they have been exposed in the marrow during the first period of their development.

The Macropolycytes of Addison's Anaemia.

1. The Type I macropolycyte is frequently found in Addison's anaemia, and here again it is necessary to consider the general behaviour of the polymorph in this disease. As we have seen above, in the infective state the polynuclear count is left-handed. Many uncomplicated cases of Addison's anaemia, however, show the remarkable state of having an increase in the cells of Classes IV and V, and the count appears to be actually right-handed, as the following figures show:

	I.	II.	III.	IV.	V.
Normal ...	10	25	47	16	2
Case 1 ...	8	20	39	22	11
Case 2 ...	6	27	40	22	5
Case 3 ...	7	20	44	24	5
Case 4 ...	7	16	29	39	9
Case 5 ...	20	31	17	16	16
Case 6 ...	16	22	32	16	14
Case 7 ...	10	15	38	24	13
Case 8 ...	12	34	26	20	8
Case 9 ...	6	20	42	20	12
Case 10 ...	8	24	30	26	12
Case 11 ...	6	18	36	24	16
Case 12 ...	6	20	40	26	8
Case 13 ...	14	28	23	20	15
Case 14 ...	12	28	36	18	6

This condition is not seen in any microbial disease, and is very strong evidence against Addison's anaemia being due to an infection.

It has been pointed out above that no class is made in the polynuclear count for cells with more than five lobes in their nuclei, because cells with more than five lobes are rare in normal blood, and if any are found they are placed in Class V. In Addison's anaemia, on the contrary, hypersegmentation of the nucleus in cells of normal size is frequent. The nucleus may have six, seven, eight, or even ten or more divisions. Plate III, Figs. 1 to 11 are examples of this nuclear hypersegmentation in cells of approximately normal diameter. All gradations in size are seen until the macropolycyte is reached. Plate III,

PLATE IV.

Macropolycytes of the megakaryocyte type (Type II), found in cases of Addison's anaemia. ($\times 1,000$ diameters.)

PLATE III.

Figs. 1 to 11.—Polymorphs showing hypersegmentation of the nucleus from cases of Addison's anaemia. ($\times 1,000$ diameters.)

Figs. 12 to 16.—Macropolycytes of Type I found in Addison's anaemia. ($\times 1,000$ diameters.)

The photomicrographs illustrating this article are by C. F. Hill and W. E. Cooke. Plate I is reproduced from *Elementary Haematology* by kind permission of Messrs. Charles Griffin and Co. Plates II, III, and IV are reproduced by kind permission of Dr. Paul Chevallier, editor of *Le Sang*.

Figs. 12 to 16 are examples of the Type I macropolyocyte. Its frequency in Addison's anaemia contrasts very sharply with the rarity in health and in infective conditions, and the cause of its appearance is not the same.

There are several possible causative factors. Polymorphs of normal size with hypersegmented nuclei accompany the Type I macropolyocyte in this disease, and the first thoughts are that there is some biochemical change in the plasma that prematurely ages the polymorph and alters its life-history; the second, that the mechanism for the elimination of old polymorphs is in abeyance. The third reasonable thesis may be advanced that the polymorph is inherently abnormal owing to a defect in its parent, the haemocytoblast, or in its environment. Possibly, too, there is a single biochemical defect that is responsible for all three conditions. The liver diet alters the polymorph picture in a few days. Macropolyocytes and polymorphs with hypersegmented nuclei disappear, and at the same time the morphologically and probably also chemically abnormal cells of the haemoglobiniferous series are replaced by cells of normal appearance.

2. The Type II or megakaryocyte type of macropolyocyte is found only in Addison's anaemia, and appears in blood films during serious relapses. Almost all the cases in which it has been found have had erythrocyte counts of less than 1,000,000 per c.mm., and before the era of liver treatment all died within a short time of its appearance. After death these large cells are found, as Gulland and Goodall (1925) pointed out, in the liver in association with islets of megaloblasts and in the pre-aortic lymph glands. Plate IV illustrates the variations in this type of cell. The cells are large, measuring up to 24 or more microns in diameter, and resemble the megakaryocyte of the marrow. The nucleus is gnarled and may be of the simple horseshoe type, or may have fourteen or more segments. The coarse cytoplasmic granules are not all oxyphil, but mixed with varying numbers of azurophil granules.

The cell does not resemble any embryonic or post-natal blood stream cell, nor is it an accurate replica of the megakaryocyte of the marrow. The life-history would appear similar to that of the polymorph in that it commences its circulatory existence with a single-lobed nucleus, which later becomes segmented. Its length of life we do not know, nor have we any means of calculating it. There is considerable doubt about its origin. It may be an expression of the abnormal reversion to embryonic type of the marrow haemocytoblast as are the haemoglobiniferous cells in Addison's anaemia. On the other hand, the cell may not arise in the marrow but originate in the mesenchyme descendants in the liver and haemolymph glands that have undergone abnormal myeloid metaplasia.

CONCLUSIONS.

1. The macropolyocyte found in health and in infections has no diagnostic nor prognostic significance, and is due to the accidental prolongation of the lifetime of a neutrophil polymorphonuclear leucocyte.

2. The causation of the appearance of the Type I macropolyocyte in Addison's anaemia is closely related with the factors responsible for the production of hypersegmentation in the nuclei of the polymorph. Whether the factor is a biochemical change in the environment or an inherent defect in its parent cell is not known.

3. The Type II or megakaryocyte type of macropolyocyte may have its origin in the marrow, or arise from the endothelium of the liver and haemolymph glands. In the first case it is the product of abnormal reversion of the haemopoietic tissue, and in the second of abnormal myeloid metaplasia.

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CANCER AND THE GENERAL PRACTITIONER.*

BY

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MANY of the papers on the subject of cancer might lead the casual reader to imagine that early diagnosis of this condition is never effected except by the writers of the papers in question, and that practitioners as a body fail signally in their duty to the community. It is often forgotten that the early diagnosis of a case of cancer demands the co-operation of an intelligent and alert patient, ready to seek immediate advice, with a doctor competent to appreciate minor departures from the normal and ready to give immediate advice. The patient, however, may be unobservant; or he may not bother, until it is far too late, about a condition which seems to him—usually because it is not painful—of little or no importance. Conversely, the doctor sometimes lets the patient down by making avoidable mistakes.

Generally, I think, mistakes arise from one of two causes: The first is imperfect examination, which may be the fault of the patient or the doctor. The patient, for various reasons, may refuse to be thoroughly examined, or the doctor may continue to prescribe for his patient without attempting any real examination. He may, for instance, give treatment for "piles" without examining the rectum, or give medicine for abdominal pain without inspecting the abdomen. The other fruitful source of error is want of thought—failure to attain, by a careful summing-up of symptoms, the clear perspective which would lead to an immediate diagnosis.

Unfortunately there is no royal road to a diagnosis of cancer—no short cut, as there is in the case of syphilis. But we have many valuable aids to diagnosis, both bedside and laboratory. In the former category are such instruments as the proctoscope, the sigmoidoscope, and the cystoscope, which are used far too rarely by practitioners,

though in many cases they are easy to use, easy to maintain, and most invaluable in the information they give.

In the latter category are tests for occult blood in the stools, or for free acid in the stomach. But it is most important to remember that these are only aids; they must never be considered apart from their context—the patient. We must guard ourselves against the danger of getting lost in a laboratory maze; above all, we must not attach undue importance to negative findings, especially to those of the x-ray examination. One often finds that both patient and doctor are lulled into a feeling of security by a radiologist's report that there is nothing abnormal to be seen, which is wrongly taken to mean that nothing abnormal is present.

The subject of early diagnosis embraces a consideration of the preventive treatment of cancer by the early detection and prompt treatment of conditions that we know to be precancerous. I still often see patients with warts of the lip and tongue, papillomas of the bladder, small rodent ulcers of the face, or small tumours of the breast, who have been told that they need not bother about them unless they become troublesome. By the time such things become troublesome they are troublesome indeed.

Periodical Medical Examination.

I will refer briefly to the controversial topic of periodical medical examinations, although why it should be controversial I cannot imagine. We all go to the dentist at regular intervals; we are all examined for life insurance from time to time; some of us have our drains inspected periodically; others have their electric wiring tested. It does not seem to me unreasonable, therefore, to carry this established principle to its logical conclusion and to undergo periodical medical inspection. I should like also to see much more intelligent and sustained instruction of our youth in the elements of physiology, for there can be no question that a more perfect knowledge on the part of the public of normal physiology would result in a quicker appreciation of any departure from the normal standard, and greater readiness to seek advice. At present people know far more of the anatomy and physiology of

* Abstract of a lecture given at Leeds under the auspices of the Yorkshire Council of the British Empire Campaign.