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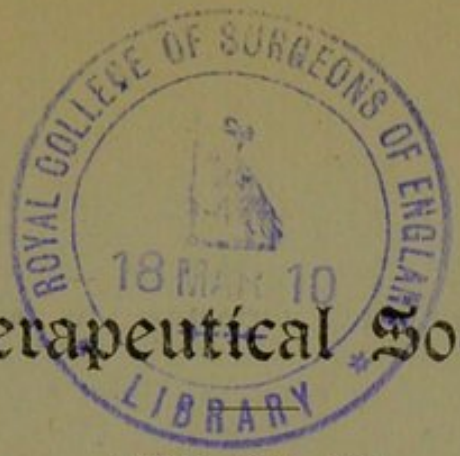

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SOME EXPERIMENTS UPON DRUGS WHICH ARE SAID TO INCREASE THE NUMBER OF LEUCOCYTES IN THE BLOOD.

BY

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WITHOUT entering into great detail upon the reasons for experiments of this nature, a few words of introduction seem necessary.

The functions of the leucocytes of the blood in health are even yet but imperfectly understood, but one of them is held to be that of protecting, or helping to protect, the body from certain infections, particularly those due to micro-organisms. In some cases the microbial attack is local, and the leucocytes seem able to engulf or devour the bacteria, the process being termed phagocytosis; Metschnikoff is the strong champion of this view of leucocytic function. In other cases the infection is general throughout the body, though the microbes themselves may still be local. For example, in pneumonia, where the pneumococci seem confined to the lungs, and yet the whole system is affected by the poisons they produce. In yet other cases the microbes themselves are disseminated everywhere, as in cases of septicæmia; and in other cases, such as scarlet fever, the body is poisoned in some way, though no microbes have been found. Probably the nature of the process of

recovery is not always the same in these different varieties of infection, but in some at least, for instance, in pneumonia, the leucocytes appear to play some part. In pneumonia and in cases of deep-seated pus formation, to take two examples, there is frequently a great increase in number in the leucocytes in the blood; instead of the more usual 5,000 to 10,000, they may number 30,000, 50,000, or even more, to the cubic millimeter. This can hardly be the case unless they are actively taking part in resistance to the infection, and in helping to restore the patient to health. How they do this is quite uncertain. Metschnikoff believes his phagocytic theory covers every case. Walker, following up Ehrlich's theory of immunity, believes that they act in another way, and a word or two may be said in regard to this. To put the matter in a somewhat crude form, it seems that when a human body is infected by a microbial poison or toxin, that human body may contain plenty of the antidote or antitoxin, and yet may perish unless there be something else present as well. This something else is variously styled; one of the names for it is "complement," and the "complement" is regarded as a sort of go-between or coupling, which attaches itself both to the "toxin" and to the "antitoxin," and enables these two to neutralise each other. Now Walker has published experiments which indicate that the "complement" is derived from leucocytes, and he believes that this function of the leucocytes' complement formation, is most important, in many cases at least, of recovery from infectious diseases.

I do not wish to enter further into the complicated question of immunity; I think I have said enough to show how important it may be to know of therapeutic agents by which an increase in the leucocytes of the blood may be brought about. Of course, it does not follow that because a given drug will produce an increase of leucocytes, it will necessarily be of benefit in any particular disease. A drug, *x* for example, might be capable of doubling the number of leucocytes, or of doubling the amount of complement, but it might be that the whole of this increase was necessary in order to neutralise the other effects of the drug itself, leaving no surplus of either leucocytes or complement to deal with the infective material of the disease from which the patient was suffering. On the other hand, it seems not impossible that a drug might be discovered whose action was to stimulate leucocyte and complement production to such an extent that the patient might have an increased power of resisting and overcoming the infective process. In conditions such

as infective endocarditis, such a drug, if known, would be invaluable. The first point, and that in which this Society will be chiefly interested, is to discover what drugs will increase the leucocytes in healthy man; and it will be a subsequent research to test the value of this action in particular diseases. To take an analogy, the discovery of those drugs which will produce diuresis was important in itself; it is a subsequent application of this discovery to use those drugs in medical cases where increased urine secretion seems indicated; the present experiments were confined to the drug production of increased leucocytes in healthy man.

A certain amount of work has already been done in the same direction. Mayer, in Von Jaksch's clinic in Prague, reports from a series of experiments lasting nine days, an average increase in leucocytes of over 75 per cent. on the three days when nuclein was administered. Halm, of Munich, and Hofbauer, of Vienna, state that they have obtained similar results, with none but beneficial effects. Batty Shaw, using an emulsion of ¼ grain of cinnamate of soda in sterilised normal saline, and injecting it into cats, caused a leucocyte increase of from 31 per cent. to 192 per cent. Richter and Spiro have obtained similar results.

I have other references to the use of turpentine, potassium chlorate, pyrodin, collargol, and ether, where injections hypodermically produced similar slight increases, but in all cases in animals. The fact that the experiments were made on animals is important, because it is well known how readily the numbers of leucocytes may be made to vary in them, even by very slight causes. It is important, further, that the increase was always slight, for the normal figure is well known to be variable, and the increases in many of the recorded cases, even on animals, were almost within the limits of normal variation.

The present experiments were all carried out upon myself, and I cannot find reference to others of a similar nature carried out upon a healthy man. I was living my usual life, with the usual meals all the time, and previous to the drug administration I counted the leucocytes in the morning, at midday, in the evening, and at night, over a week's period, in order to find the healthy variations. These were considerable, namely, from a minimum of 5,000, to a maximum of 13,000 per cubic m.m. I conclude, therefore, that no leucocyte count following a drug administration in myself, and not exceeding 13,000, can be regarded as an increase due to the drug.

I then carried out a series of experiments with nuclein, kindly supplied by Parke, Davis & Co. This was the same as that which Mayer has stated to produce leucocyte increase in cats. For a week I took 1 dr. of their nuclein solution No. 2 four times a day, counting the leucocytes at intervals. They never exceeded 11,000 and were usually far less. For the next week I took 2 drs., the full dose, in the same way, with exactly the same result. I then took their dry nuclein in capsules, four capsules a day for the first week, with a maximum count of 13,125; eight capsules a day for the second week, with a maximum count of 11,875. No ill effects followed, there was at no time an excess of leucocytes in the blood. I then used their nuclein solution No. 1, and injected it hypodermically in increasing doses—10 c.c., 20 c.c., and 30 c.c., on successive days. It was painful, there was a slight local erythema upon the fourth day, and much local itching of the skin, but no leucocyte increase at all. I could not conclude that nuclein, either by mouth or hypodermically, caused any artificial leucocytosis.

I next tried injection of 5 grains of sodium cinnamate suspended in normal saline, as Batty Shaw had done, but the leucocytes showed no increase exceeding the maximum found in myself under normal conditions.

I then tried collargol hypodermically in a similar way, as the result of seeing a reference to experiments with it in Germany. The collargol was sterilised by boiling, and full aseptic precautions were taken, and the results were as follows:—

After injecting 15 mgs. no untoward effects occurred, but there was no increase in the leucocytes. After injecting 30 mgs. there was no rise for ten hours afterwards, the leucocytes then reached 14,375, which is slightly in excess of my healthy maximum; they rose to 16,250 at the end of 24 hours, and I then began to feel unwell, with lassitude, pain in the back and limbs, and headache, but without loss of appetite, and without loss of pleasure in tobacco smoking. In which two latter respects the condition differed entirely from influenza, which the other symptoms at first suggested. I had no shivering. My temperature was 99° 30 hours after the injection; at 40 hours it was 101°; at 48 hours, 100°; at 60 hours, again normal. The arm did not become inflamed, though it was tender at the site of inoculation; the headache, which was of the variety which is absent when the head is kept absolutely still, but is very evident on the slightest movement, persisted for four days, for

the first two of which I could not work. The leucocytes reached a maximum of 22,187 at 30 hours from the inoculation, and then rapidly fell to normal.

This was the last experiment I did upon the subject under discussion. It frightened me and those about me; and it has impressed upon me very much the danger of taking hypodermic injections. The drug, collargol, certainly was followed by leucocytosis, and to that extent was satisfactory. But the concomitant symptoms render it unlikely to be of benefit in treating a patient who is already ill.

I am afraid, therefore, gentlemen, that my experiments add little to your knowledge, though the personal experience is, I think, worth telling. None the less, I still believe some patients might be benefited could we find a non-noxious leucocyte-increasing drug. I think experimental results in animals cannot be inferred to be true of man, as I have shown in the case of nuclein. I think that hypodermic injections in bulk are highly dangerous, and to be avoided in the case of little known drugs, such as collargol; and I come to the Therapeutical Society for information or for suggestions for further investigations upon drugs which they think might stimulate leucocyte production without concomitant noxious effects, and which may be given, not hypodermically, but by the mouth.