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OBSERVATIONS ON THE OPSONIC INDEX OF PATIENTS UNDERGOING SANATORIUM TREATMENT FOR PHTHISIS,

WITH SPECIAL REFERENCE TO THE EFFECT OF EXERCISE.

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IN the summer of 1904 Professor Wright was kind enough to examine the blood of several of the patients in this sanatorium, and to estimate their opsonic power against tubercle. It was at once seen that certain differences in opsonic index were associated with certain differences in clinical character, and some cases, which at first appeared to be exceptions to this view, showed by their subsequent course that they were not. The opsonic index in these cases proved a more correct indication of their true character than their clinical appearance and previous history.

These blood examinations were made with the view to the use of "new" tuberculin, and since then a series of cases has been treated with this remedy with encouraging results, which we hope shortly to publish.

The work of estimating the opsonic index is now done at the sanatorium, thanks to Dr. Wright and Captain Douglas, I.M.S., who very kindly took much trouble to teach us the technique, and it is therefore possible to make a large number of observations every week.

Since the word "opsonin" is still a new one, we may, perhaps, be excused if we explain briefly what is meant by "opsonic index," and how it is estimated. It has been shown by Wright and Douglas¹ that the rate of ingestion of bacteria by polynuclear white blood corpuscles depends upon the extent to which the bacteria have been previously acted on by some substance existing in serum to which the name "opsonin" has been given. There appears to be a separate opsonin for each

variety of bacteria. The presence of opsonin is determined, and its quantity in a given serum is estimated, by the rapidity with which polynuclear white corpuscles devour bacteria which have been exposed to the action of the serum in question.

The experiment is performed by mixing together equal quantities of (1) serum-free corpuscles obtained by washing blood in 1 per cent. citrate of soda in normal salt solution and afterwards in normal salt solution only, (2) an emulsion of tubercle bacilli, and (3) the serum to be tested. The mixture is incubated at a temperature of 37°C. for twenty minutes, and then a film is prepared and stained in the usual way with carbol fuchsin and methylene blue. The average number of bacilli ingested by each polynuclear white corpuscle is ascertained, and, taking the average number ingested when the serum of a healthy man is employed as unity, the opsonic value of any other serum is expressed in terms of this. Thus, if the average number ingested by each polynuclear white corpuscle of healthy serum is 5, and with the patient's serum is 4, then the healthy man's opsonic value being called 1, the opsonic value of the patient will be 0.8; on the other hand, if the experiment with patient's serum gives an average ingestion of 7 then his opsonic value will be 1.4.

It was noticed at the outset that our results, while showing the same range of variation after tuberculin injections, were, taken on the whole, much lower than those obtained by Dr. Wright, and we were quite unable to endorse the view

expressed by Dr. Urwick in the *BRITISH MEDICAL JOURNAL* (July 22nd, 1905) that "the opsonic power of the majority of patients suffering from pulmonary tuberculosis is higher than normal." It seemed that either our controls were higher than those of Dr. Wright and Dr. Urwick, or our class of patients differed from theirs. A comparison of our results with results obtained in Dr. Wright's laboratory by a simultaneous examination of the same blood showed that our control only differed from Dr. Wright's by 0.05. Clearly, therefore, the discrepancy could not be due to a difference in controls. While still seeking for an explanation, it occurred to us that the samples of blood sent to Dr. Wright had always been collected at 2.30 p.m., in time to catch the afternoon post, while the samples examined by us were taken at 9 a.m. A series of observations was then made to ascertain what variations, if any, took place during the day, and the times chosen were those which fitted in with the routine practised in this sanatorium. All patients are visited before they rise in the morning, and are given directions as to how they are to occupy their time until noon—that is, either by walking

(and, if so, how far) or by resting. The temperature is recorded immediately the patient comes in, and he then rests in a long chair until 1 o'clock. As is now well known, even healthy men show a considerable rise of temperature after exercise, and the rise is followed, on resting, by a speedy fall. The same phenomena occur, as a rule, in a case of phthisis, and an exercise temperature of 100° F. recorded at noon will usually fall to 99° or 98.8° F. at the end of rest hour.* The times chosen were therefore 9 a.m., noon, and 1 p.m., and to complete the list, an observation was also usually made at 6 p.m. the evening before.

A series of these observations is shown in the accompanying chart, and it will be seen that in all "walking" cases, except one, the 1 p.m. observation shows a much higher index than the observation made at 9 a.m., and in cases that are resting there is practically no variation throughout the day. The explanation of this, no doubt, is that the exercise leads to a slight degree of auto-inoculation, which is followed by a very transient rise of opsonic index. The one exception, No. 3, was a patient with a nearly-healed lung and a small, healing ulcer in the larynx. He showed less tendency to rise after walking, probably because his lesion was so small that auto-inoculation could only take place to a very slight extent. This series at once explained the difference between Dr. Wright's results and ours.

From this series, which has been quite free from any conflicting results, we conclude that it is a matter of great importance in estimating the effect of injections of tuberculin, or of any particular form of treatment, that the observations should be made at a time when the opsonic index is at its ordinary level, and undisturbed by recent exercise. It is therefore our practice to take all samples of blood at 9 a.m., though, if the patient is resting, the time is obviously unimportant. We have had no opportunity of observing whether exercise in a case of "surgical" tubercle is followed by a rise of opsonic index, but we should expect that, where the focus was small and the chance of auto-inoculation slight, there would be only a slight rise or none, as in the laryngeal case referred to above. We have never found that a patient's temperature gave any clue to the level of his opsonic index.

In view of the fact that so much of the present-day sanatorium treatment is admittedly empirical, and much of it difficult to explain on any scientific grounds, it was hoped that useful knowledge might be gained from an observation of the opsonic indices of sanatorium patients. We think that the series of observations shown here is at least an abundant justification of the routine usually followed, and explains why patients so often make rapid progress as soon as they are well enough to walk without harm. But, in a case where active disease is still present, the decision whether walking is likely to be beneficial or otherwise is one of the most difficult that the sanatorium medical officer is called upon to make, and for which the widest experience is necessary.

As Dr. Urwick has pointed out, a case of active phthisis, shows an alternating high or low opsonic index which he believes to indicate alternating positive and negative phases following auto-inoculation.† If this is the case—and all our observations lead us to endorse his view—it is clearly important that a patient should rest during his negative phase, and probable that he will benefit by walking when his opsonic index is high, since, as shown by Wright and Douglas,‡ the opsonic pressure is always reduced at the focus of infection even when the opsonic pressure of the blood serum is high. We hold therefore that, taken into consideration with the clinical condition of a patient, a knowledge of his opsonic index will materially help in choosing the routine that will give him the greatest benefit.

We are inclined to think, but our observations are at present too few and the time that has elapsed too short for us to speak with any confidence, that the opsonic index and its range of variation, is a valuable factor in making a prognosis. Wherever there is active disease, either in an early case that has not been long under treatment, or in a case that has not responded to treatment, the opsonic index shows a wide range of variation, but when the disease becomes less active, the opsonic index settles down to a level which shows scarcely

* It is interesting to remember that it is only recently that this rise of temperature after exercise has been generally recognized, while a "normal" temperature on waking in the morning is now regarded as dangerously high, and in most sanatoriums is taken to indicate the need for complete rest during the day.

† Dr. Wright has shown that the rise in bactericidal power which follows inoculation with a bacterial vaccine is preceded by a negative phase of lowered bactericidal power of varying duration.

any variation from day to day (in blood drawn at 9 a.m.), and this level varies widely in different cases. In one case, after initial variations ranging from 0.5 to 2.4, the opsonic index after six weeks settled down to an almost constant 1.0, the observations made every three days being as follows: 0.975, 1.1, 1.0, and 1.07. Another case settled to a mean level of 0.8. Our experience tends towards the view that the case that settles to an opsonic index much below 1.0 is the case that becomes "chronic," that recovers to a certain extent, but that can only maintain that degree of recovery while living under sanatorium conditions. We believe, on the other hand, that a case which shows a steady opsonic index of 1.0 or over is the case which makes a complete recovery if favourable conditions are maintained for a sufficient time.

It is in cases of the first group, with an opsonic index that settles to a level of 0.8, or even lower, that we have had the most encouraging results with injections of tuberculin, and even in cases of the second group we believe it is possible to shorten the time necessary for recovery by artificially raising the opsonic index by the same means.

We are led to publish these observations because we think that, few as they are, they are sufficient to show that a knowledge of the opsonic index of a patient can be of great interest and help to those responsible for his care, since it to some extent explains the rationale of much that has hitherto been empirical in the routine of sanatorium treatment. The process of estimating the opsonic index is slow and tedious, and this prevents any rapid advance in knowledge. It is essential that large numbers of observations should be made, and the curves of variation under varying treatment carefully plotted out. It is only when the work is much more widely taken up than it is at present that any rapid progress will be made. Perhaps these few very incomplete observations may prove sufficient to induce others to take up the work.

CASE I.

Very chronic—extensive disease of lungs. Physical condition fair.

CASE II.

Very chronic lung disease—has responded in a very satisfactory manner to sanatorium treatment.

CASE III.

Nearly healed lung. Small ulcer on left vocal cord. Physical condition good. Opsonic index originally 0.73—now rising after injection of 1/600 mg. of tuberculin on September 17th.

CASE IV.

Chronic lung disease. Physical condition fair.

CASE V.

Chronic lung disease. Physical condition good; C. and D. record negative phase following injection of 1/1,000 mg. tuberculin on September 30th, opsonic index previously 1.0.

CASE VI.

Opsonic index rising after injection of 1/1,000 mg. tuberculin on August 31st; opsonic index before injection 0.68.

CASE VII.

Double psoas abscess, healing sinuses. Injection, 1/750 mg. tuberculin on September 22nd.

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ON A HITHERTO UNDESCRIBED CHANGE IN THE URINE OF PATIENTS SUFFERING FROM NEPHRITIS.

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In a preliminary paper (*BRITISH MEDICAL JOURNAL*, 1903, vol. 1, p. 190) Armand Ruffer and M. Crendiropoulos showed that the injection of the urine of man, or of certain animals, into rabbits rendered the serum of rabbits haemolytic for the blood corpuscles of man or of that species of animals the urine of which had been injected. In another paper (*Journal de Physiologie et de Pathologie*, 1905, p. 820) the same authors and G. Calvocoressi showed that the substances (lysogens) producing a haemolytic serum dialysed slowly, were totally insoluble in ether and almost insoluble in alcohol, were precipitated from urine by saturation with ammonium sulphate or lead acetate, showed great resistance to the action of heat, but were quickly destroyed by acids or alkalis. They disappeared