A Clinical Lecture

ON

OPSONINS IN RELATION TO THE SPECIFIC TREATMENT OF TUBERCULOSIS.

DELIVERED AT THE MEDICAL GRADUATES' COLLEGE AND POLYCLINIC.

By J. EDWARD SQUIRE, C.B., M.D.,

PHYSICIAN TO THE MOUNT VERNON CONSUMPTION HOSPITAL.

THE essential potentialities of living matter have been defined by the physiologist from a study of life in its simplest forms. The complex activities of the more specialized tissues of the higher animals are but developments of the simple processes carried out in the protoplasm of an amoeba. Composed of protoplasm, the cell elements of the tissues and the wandering cells of the body have the power of assimilating material and converting it into protoplasm, thus nourishing themselves and growing. In the process of producing protoplasm and as an aid to this, other substances (by-products, as it were) are formed, and either stored up or excreted. The cell is, however, dependent for its nourishment upon supplies from outside, which, in the case of the body cells, must be brought to it by the blood stream. Its activity, moreover, is largely excited and the nature of this determined by external stimuli, which also may reach the cells by way of the blood. Thus, though we look to the cell as the active agent, we must also study the constituents of the blood under different circumstances if we would investigate the causes of the various modifications of cell activity. In the higher animals the metabolic power of the cell is developed and specialized in the component cells of the various organs—thus the brain cell and the liver cell, for example, perform different metabolic functions. How far any individual cell may, by suitable pabulum and stimulus, have its normal metabolic activities further developed or altered it is impossible to say; the metabolic potentiality of all cells is presumably essentially equal, but in the ordinary course specialization only results from the slow development of generations.

The special metabolic activity of the body cells is determined, first, by the nature of the cell, and then by the special stimuli present in the blood and lymph, these stimuli varying under different conditions. Thus the blood from the duodenum during digestion contains certain substances (hormones) which act as stimuli on the cells of the pancreas and call forth the secretion of pancreatic juice.¹ So also hormones in the blood of the pregnant woman—probably produced by the development of the fetus *in utero*—stimulate the cells of the mammary glands to the secretion of milk. It appears also that the same cell—for example, a leucocyte—may vary the direction of its metabolic activity and secrete different products under the influence of different stimuli.

In disease we may have innumerable modifications of cell activity, leading to structural abnormalities and abnormal metabolic products which are (or cause) the manifestations of disease. These perverted activities, like the functions performed in health, must remain within the limits defined by the potentialities of living matter as determined by the physiologist.

Pathology is, after all, as I have indicated, only physiology gone wrong; and in examining the somewhat intricate nature of the defensive processes which take place in the body when attacked by disease we must constantly bear in mind the investigations of the physiologist.

The physiologist has shown that the cell is what may be termed the "vital unit" of the body: the cell elements of the tissues are the active parts and alone able to perform vital functions.

Starting from the physiologist's recognition of the cell as the vital unit, the cellular pathology of Virchow is the natural evolution. The perverted activities of the cells in disease, leading to tissue changes in the organs, become intelligible when we realize the power of the cell to respond to stimuli of various kinds; and the examination of the blood in disease is a necessary investigation, not only in respect of the different varieties of leucocytes, but

with regard to the constituents of the plasma, which may act as stimuli to the cells.*

As the hormones stimulate secretion, so in somewhat similar manner does the presence in the blood of morbid bacteria or their products stimulate the leucocytes or other body cells to specific activity of a defensive nature. The study of immunity is largely concerned with these stimuli and the consequent reactions in the body cells. Bacteria produce their ill-effects in the body by the secretion of substances poisonous to their host, either excreted by the micro-organisms (exotoxines) or retained in the body of the bacterium (endotoxines), and only set free on its death and disintegration. The natural inference is, therefore, that bacterial diseases may possibly be combated in two ways:

1. By the destruction of the bacteria which produce the toxins.
2. By the destruction or neutralization of the toxins which are formed.

The treatment of tuberculosis by antiseptics—creosote, guaiacol, iodo, etc.—is an attempt to carry out the first of these plans of defence. Treatment by antitoxines—such as antidiphtheritic serum—is an example of the second method.

Let us briefly examine these two methods of defence in the light of modern experience and research.

One great drawback to the first defensive method is the difficulty in finding an antiseptic which is poisonous to the invading bacteria without being harmful to the body cells.

Though some bactericidal property has been attributed to the normal (healthy) blood serum, this is obviously insufficient to destroy many bacteria, otherwise infection would not occur. More particular attention was directed to the body cells, and especially the leucocytes, as agents in the destruction of the invading micro-organisms. The multiplication of leucocytes in the immediate neighbourhood of the disease-causing bacteria suggested that this leucocytosis was a protective effort—a massing of the defensive forces at the point of invasion. Landerer's treatment of tuberculosis by cinnamic acid was an attempt to increase leucocytosis; it is undoubtedly useful, and appears to favour fibroid tissue formation and localization of the disease centres. A further step of great importance was the observation of Metchnikoff, that certain cells may be seen to engulf and absorb bacteria—phagocytosis. This suggested that the cells might of themselves be able to protect the body from the effects of bacterial infection so long as their vitality was unimpaired, and that treatment should aim at strengthening the resisting power of the body. The hygienic or sanatorium treatment of consumption illustrates this plan of campaign.

So far, however, the effect of the serum in stimulating and determining the activity of the cells had not been sufficiently taken into account. The clinical history of infectious diseases shows that after recovery from an attack of one of these complaints the individual is, for a time at least, less susceptible to infection from the particular disease from which he has suffered. There is an acquired immunity which presumably results from the disease, or is produced in the body by the disease processes. The exact nature of this protective condition within the body, the nature of immunity, has in recent years been the subject of much research. Briefly, the facts already observed may be summarized as follows:

The bacteria, having gained entrance into the body and having found conditions suitable for their development, multiply and become sufficiently numerous to poison the blood with their toxins. After a time the further production of the poison may cease and the illness is over.

The simplest explanation seemed to be that the micro-organisms produced and excreted a poison which not only caused illness of the host but which was poisonous to themselves. Thus, when by reason of the multitude of the bacteria the poison production became great, the bacteria themselves were destroyed by the products of their own activity. Since, after the attack is over, the individual is insusceptible to infection from the specific bacterium which causes the illness, it would seem that the poison, whatever its nature, remained in the body for some considerable time; not in sufficient quantity to

* Since this was written I have read the excellent articles by Dr. Harry Campbell in the *Lancet* on the Role of the Blood Plasma in Disease.

affect the host, but enough to prevent the development of any small number of these particular micro-organisms which might enter the body. It was evident that the poison was specific, for one disease does not protect against one of another kind.

The search for this substance which is the cause of the specific immunity has engaged the attention of many of the most accomplished scientists, and the results already obtained, though incomplete, are interesting and valuable.

The matter is by no means so simple as it at first appeared. The bacteria certainly produce some substances which are injurious to the host. These toxins may, as before mentioned, be excreted (exotoxins), or may remain in the bodies of the bacteria to be set free only on their disintegration (endotoxins). In any case the effect of the toxine is to stimulate the tissues and leucocytes of the host to defensive reaction, resulting on the one hand in tissue changes, and on the other, in the production of antitoxines (which neutralize the toxins) and in substances which destroy the bacteria. The leucocytes are stimulated by the toxine to a protective metabolism by means of which the toxine is anchored and held fast, and the metabolic by-product or side-chain (Ehrlich) of the cell, which fixes the toxine, is as it were thrown out of action. This results in over-production of this particular by-product (receptor) by the cell; some of this material may be thrown off, and, floating in the plasmas, will anchor and fix any toxine present in the blood. The serum thus comes to contain "antitoxine."

In the case, however, of bacteria (like the tubercle bacilli) which produce endotoxins, no toxine or very little will be present in the blood until the bacteria die and are disintegrated. The reaction processes of the cells will, in such case, be mainly directed towards the destruction of the bacteria. Various by-products will be produced by the cell metabolism. Some of these (agglutins) clump the bacteria, and render them less active though they are not killed. Others (lysins) dissolve the bacteria, thus destroying them. These, however, cannot act by themselves; they require the assistance of a substance (complement or alexin) normally present in the serum. Over-production of the cell products mentioned above results in these being thrown off by the cells into the plasma, forming immune bodies which, in the presence of the bacteria, will combine with the complement of the serum and cause the destruction of the bacteria. Thus, the special metabolic products of the cells require the assistance of some constituent of the plasma in order to destroy the bacteria and their products.

The antitoxines, agglutins, lysins, and immune bodies are specific for each kind of bacterium; the complement in the serum is, however, general. When bacteria are introduced into the circulation some are at once destroyed by the by-products of the cell metabolism (side-chains of Ehrlich) acting with the complement in the serum, and as soon as intermediate bodies (immune bodies, etc.) are formed and thrown off into the blood stream still more can be destroyed. But the complement is soon used up, and it is necessary to wait for a fresh supply. The agglutins keep the bacteria inert until this fresh supply is formed.² It seems probable that the leucocytes (phagocytes) are unable to assimilate and destroy the bacteria until these have first been killed by the action of the intermediate bodies and the serum complements.

Wright³ found that the phagocytic power of the leucocytes with regard to special bacteria differed considerably between animals immunized against the special micro-organism and those not so protected. He found also that the proportionate number of tubercle bacilli which each leucocyte of a healthy individual could enclose and disintegrate was greater than that which the leucocytes of a tuberculous individual could so dispose of. If, then, it is possible to estimate the relative phagocytic power of the leucocytes we have a means of estimating the resisting power of the individual. In the case of the tubercle bacillus we have the low resisting power shown in the tuberculous individual, a higher degree of resistance in the healthy individual, and a still higher resistance in the specially immunized animal.

By some careful observations Wright proved that in the absence of serum leucocytes did not absorb any bacteria, and that the phagocytic capacity of the leucocytes depends upon the serum in which they are living, and not upon any differences in the cells themselves. The phagocytic capacity towards tubercle bacilli of leucocytes from the

blood of different individuals, healthy or tuberculous, is practically equal for all when the same serum is used for all the observations. On the other hand, the leucocytes from the same individual vary in their phagocytic capacity according to the serum (healthy or tuberculous) in which they are tested. It is evident, therefore, that something in the serum either stimulates the phagocytes to action or so acts upon the bacilli as to make them more readily absorbed by the cells. This something is apparently produced in or added to the serum as a result of irritation by the special bacterium. As a sequence of infection by a special bacterium some protective substance is produced (specific for each kind of bacterium) which renders the bacteria susceptible to the phagocytic power of the cells, and, as it were, prepares them for eating.

This something Wright calls an opsonin (*ὀψωνεῖν*—to prepare a feast). We may for the present take it that the production of opsonins is on the same lines as the production of other antibodies, from side-chains of the leucocytes formed in response to the specific stimulus of some bacterium or its toxine. It may be that the opsonin and the immune body are one and the same substance. Against this theory we have Wright's statement that the opsonin is destroyed by heat (60° C.), whilst the immune body is undoubtedly thermostable. Some recent observations⁴ have, however, thrown a doubt upon the non-resistance to heat of the opsonins. On the other hand, evidence⁵ has been brought forward tending to show that opsonins are in the nature of complement; if so we shall have to modify our views as to the non-specific nature of complement. With such different suggestions as to the identity of the opsonin, we may be permitted to confess our present ignorance of its exact nature.

The great value of Wright's observations is in the application as a means of measuring the resisting power of blood to any special bacterium, such as the tubercle bacillus.

If a definite proportion of the blood serum of the individual to be tested, together with some washed leucocytes, be added to a definite quantity of a standardized emulsion of bacteria, and incubated at the body temperature for a certain time (for example, fifteen minutes), and is then microscopically examined, a number of bacteria will be found within the leucocytes. A certain number of leucocytes are examined, and the total number of the contained bacteria are counted; from this the average number of bacteria absorbed per leucocyte is obtained. This average number compared with the average similarly obtained with a serum of known resisting power to the particular bacterium in question will give the relative resisting power of the individual under observation. The point now to be considered is how to obtain a serum of known resisting power as a standard of comparison.

Wright's observations, confirmed and extended by Bulloch and others, showed that the resisting power (or phagocytic power) against any particular bacterium varies little in different healthy individuals, and is practically constant.

The serum of any healthy person can therefore be used as the standard; the phagocytic capacity of leucocytes incubated with the serum to be tested as compared with that of leucocytes similarly treated with the serum of a healthy individual gives the "opsonic index" of the serum under observation. This opsonic index represents the resisting power of the individual to the particular bacterium used in the test as compared with that of a healthy person. Thus if the average number of tubercle bacilli taken up per leucocyte in the healthy serum is 10, and the number per leucocyte in the serum of the individual to be tested is only 5, this person's opsonic index is said to be 0.5. Wright found further that the opsonic index in regard to a particular bacterium may be influenced by the injection into the body of its specific toxine. If a large dose of toxine is introduced the opsonin is used up and the opsonic index falls: with smaller quantities of toxin, a temporary fall (negative phase) is followed by a considerable rise in the opsonic index (positive phase). The body cells may thus be stimulated to produce excess of opsonin or protective substances so long as the dose of toxine is not too great. The positive phase is not permanent, in fact only lasts a comparatively short time in the case of tuberculous inoculation; the opsonic index gradually falls, though it may not fall as

low as before the stimulation. The effect of inoculations—at least in the case of tuberculosis—is not cumulative, but when the positive phase has passed off a further inoculation will cause a repetition of the phenomena described.

By a series of inoculations properly timed, the opsonic index may be gradually raised until it remains permanently higher than it was at first. Inoculations during the negative phase—the duration of which depends largely upon the dose of toxine injected—produce a further fall in the opsonic index, and no positive phase may follow; the resisting power of the individual has then been weakened or destroyed.

Acting on these observations, Wright has employed Koch's tuberculin to stimulate the production of protective substances in cases of tuberculosis, in the belief that by this means a sufficient reaction may be promoted in the body to result in the cure of the disease.

The dosage and frequency of the injections of the tuberculin are carefully regulated by estimations of the opsonic index from time to time. Wright has in this way shown that the dosage of tuberculin as employed on its first introduction was dangerously high, and has furnished an explanation of the failure of the tuberculin treatment under the old conditions.

It will be noted that Wright's work in regard to opsonins in tuberculosis consists of two distinct practical considerations:

1. The determination of the opsonic index.
2. The treatment of tuberculosis by tuberculin injections regulated according to the condition of the opsonic index.

These are distinct, and must be considered separately. The application of the determination of the opsonic index to the regulation of treatment in cases of tuberculosis has impressed the public fancy, and people talk of "Wright's opsonin treatment." We may, however, thoroughly appreciate the value of the scientific observations without necessarily agreeing with the tuberculin treatment, even when its effects are checked by observing the opsonic index.

Let us, then, examine these two questions separately with regard chiefly to, first, the practical value of a determination of the opsonic index for tuberculosis, and, secondly, the specific treatment of this disease.

1. THE DETERMINATION OF THE OPSONIC INDEX.

There seems every reason to expect that with more exact methods the determination of the specific opsonic index may become a most valuable aid to diagnosis, a definite index of the progress of a bacterial disease, and a useful means of regulating treatment.

As a means of diagnosis it is as yet unreliable, though often useful. It has been already pointed out that the opsonic index varies little in healthy persons, and when this index is found in any individual to be outside the limits of health, it is a fair inference that the individual is suffering from infection from the specific bacterium.

Certainly, if the index is very low, the person is specially vulnerable—his resisting power is small. This, however, may be a "constitutional" or inherited weakness—a predisposition only; or, on the other hand, it may be the result of infection, the opsonins and other protective substances having been partly used up in combating the invading bacteria. There is thus an element of doubt as to the significance of the low opsonic index.

Again, the opsonic index of healthy persons, though nearly constant, yet varies within certain limits, and thus we have a varying standard with which to compare the serum to be tested. In comparison with the serum of one healthy person which is taken as unity the opsonic indexes of a number of other healthy persons will be found to range from 1.2 to 0.8.

Now, if a serum to be tested is compared with that of a healthy person at one end of this limit (1.2) and the opsonic index by this standard is 0.9, the test subject would be considered free from tuberculosis; whereas if the standard serum were that of a healthy person at the other extremity of the scale, the index would work out at 0.5, and a diagnosis of tuberculosis would be justified.

It is evident, therefore, that we require a standardized serum with which to compare serum to be examined for diagnostic purposes.

The above difficulty is in part overcome if repeated

observations are made, for in many cases the opsonic index of a tuberculous subject varies from time to time, whilst that of a healthy person remains almost constant. It must be borne in mind that in a large number of undoubted cases of tuberculosis, especially in the subacute cases, the opsonic index remains within the limits of health. A patient whom I see at intervals, who in addition to extensive tuberculosis of the lungs has deposits of tubercle in other organs (testicle and probably liver and kidney), is found to have an opsonic index varying between 1.2 and 0.8, exactly within the limits found in healthy persons. This condition of the opsonic index in tuberculous patients is observed in sanatorium records.⁶

An opsonic index which is above the higher limit compatible with health is taken to indicate an excessive production of protective substances, which is presumably due to the presence of the specific irritant. It therefore denotes the specific infection with, at the same time, active defensive reaction—a condition favourable to cure.

We can as yet only say that the determination of the opsonic index in a doubtful case of tuberculosis may possibly furnish indications which might assist diagnosis; it should therefore not be neglected in doubtful cases.

Attempts have been made to utilize the opsonic index as a guide to prognosis in cases of tuberculosis.⁶ The result as yet has not been particularly satisfactory. As a measure of the progress of the disease and of the effects of treatment, repeated determinations of the opsonic index, using always the same blood as the standard of comparison, should be of the greatest advantage. The effect of treatment of whatever nature, not only of tuberculin injections, may be watched, and to some extent controlled, by an occasional estimation of the opsonic index of the patient.

We have, then, in the determination of the opsonic index, a valuable clinical aid in diagnosis, prognosis, and treatment. It cannot be said to give definite information, but new methods require practical experience of their working before their full value is developed. At present the process is too lengthy in operation for the busy practitioner to employ himself, though he can easily send up a small quantity of his patient's blood serum to be tested at one of the clinical and pathological laboratories. The drawbacks to the more general and useful employment of the opsonic index in clinical work will no doubt soon be removed.

2. THE SPECIFIC TREATMENT OF TUBERCULOSIS.

We may at once grant that if injecting tuberculin in any of its forms is a useful method of treatment for tuberculosis, Wright's improved method of employing this remedy renders this treatment very much safer and more satisfactory. I do not wish here to affirm or deny the advantages of tuberculin treatment; I merely wish to discuss the specific treatment of tuberculosis without prejudice. The determination of the opsonic index is a useful accessory to all treatment, but not an essential part of any one method. We know that bacterial infection stimulates reaction processes by which the body tends to protect or defend itself against the harmful effect of the bacteria and their products.

The morbid bacteria may be divided into two classes:

1. Those which produce exotoxines, of which the diphtheria bacterium may be taken as an example.
2. Those which produce endotoxines; the more numerous class in which the tubercle bacillus is included.

If bacteria of the first group or their toxines are introduced in suitable quantity into the body of an animal, the body cells (leucocytes) respond by producing an antitoxine; this defensive reaction can be encouraged until the blood contains sufficient antitoxine to render the animal invulnerable to a dose of toxine which previously would have proved fatal. This is "direct immunization."

The immune serum withdrawn from such an animal may be injected into another animal, which is then rendered to a large extent invulnerable to the particular toxine. This is "indirect immunization," and may be employed as a preventive or as a means of cure for that particular infection.

The successful employment of antidiphtheritic serum and

of antitetanic serum exemplifies the possibilities of specific treatment in those diseases which are caused by bacteria of the first group.

With bacteria of the second group, however, direct immunization calls for, as we have seen, a different train of defensive reaction, and the serum of an immunized animal does not contain sufficient antitoxine to allow of successful protection of another animal by "indirect immunization." An antituberculous serum analogous to the antidiphtheritic serum is, therefore, not to be looked for, so far as our knowledge of immunity at present goes. We are, then, at present thrown back on direct immunization for the specific treatment.

Koch's tuberculin and others of like nature contain the toxine of the tubercle bacillus, and when injected into the body stimulate protective reaction. To be successful either as preventive or as curative agents it is essential that the reaction results—antibodies—should be produced in excess of the toxine introduced. Here we begin to see difficulties.

In the healthy person, even the large doses which were used when Koch first introduced his old tuberculin rarely exceeded the capabilities of the body cells to produce sufficient antibodies to protect the individual from the results of the infection. When, however, from the presence within the body of active tubercle bacilli, the defensive reactions were already severely taxed, there was serious risk of the added toxines being in excess of the defensive capabilities of the cells.

Even with the much smaller doses ($\frac{1}{1000}$ mg.) now employed by Wright there is a certain risk when a person is already infected with tuberculosis. As it seems to me, we are confronted with the following alternatives: Either the bacilli and their products already in the body act as stimuli to the cells to produce antibodies—in which case, the stimulus being present, it would seem unnecessary to introduce it by injection. Or the bacilli, being localized, do not affect the general circulation, so that the general production of antibodies is not promoted because of the absence of stimulus. In this case the introduction of the stimulus into the circulation will call forth protective reaction, but this will not affect the disease focus. If the bacterial toxines cannot escape from the disease centre into the circulation, the antitoxines can hardly get from the blood stream to the seat of mischief.

It may be urged that it is desirable to have antibodies ready prepared in the blood in case bacilli escape from the centre of disease into the circulation. But if the cells (leucocytes) respond satisfactorily to toxines injected into the body they are presumably capable of similar satisfactory reaction to bacilli or toxines thrown into the circulation from the tuberculous focus.

As a general proposition it appears to be a faulty procedure to add to the toxine already in the body in order to call forth additional protective activity in the body cells. Presumably there is already excess of toxine—the evidence of disease in the individual in itself indicates this. If the defensive response in the leucocytes is insufficient it suggests either that these cells do not come under the influence of the stimulus—that is, that the disease is localized, and the toxines produced in the diseased area do not get into the blood stream—or that the cells are incapable of responding to the stimulus. In either case there seems little reason in adding toxine in the blood. If the leucocytes are already stimulated without being able to respond effectively, more toxine can only do harm. If the cells are potentially active, but the production of antitoxines (or antibodies) is small or nil, it is probable that the stimulus is wanting—in other words, that there is little or no toxine in the general circulation—nothing requiring protective metabolism in the body as a whole. To stimulate the production of antibodies under these latter circumstances is in the nature of a prophylactic measure—an active immunization of the body in view of possible general infection. This is undoubtedly a wise and useful provision against auto-infection, but it is not treating the active disease processes, and can have little effect towards curing the local tuberculosis. Wright has apparently realized this, and suggests counter-irritation and other means to increase the flow of blood through the disease area or to flood it with lymph derived from the immunized blood stream. If the leucocytes in the body generally are able to produce antibodies in response to

stimulation one would expect them to rise to the occasion if toxines should escape from the disease focus into the circulation. No doubt, however, it is a wise precaution to have these antibodies previously prepared for such an emergency.

The position appears, therefore, to be somewhat as follows: In some localities within the body bacilli are established and are producing toxines: the cells in the immediate neighbourhood are overtaxed and unable to produce sufficient protective substances to deal with the attack. The rest of the body is not infected, so that the blood does not contain the stimulus to protective metabolism by the leucocytes, and the general opsonic index remains comparatively low. We may raise the general protective power of the blood, but this hardly, if at all, affects the conditions in the disease area. Injection of tuberculin to raise the general opsonic index will not cure the disease, though it may and probably does protect the body against general infection, and may limit the spread of the disease locally. So far it is extremely valuable, especially if the individual's opsonic index was naturally low, but only as an adjunct to other treatment—such, for example, as removal by surgical means of the disease focus. I would suggest that scraping operations in surgical tuberculosis should never be undertaken without ensuring that the opsonic index of the patient is sufficiently high to guard against general infection.

There appears to be some possibility of over-stimulating the reaction powers of the cells by introducing toxines into the circulation, especially when the toxine is already present from disease. It is a physiological rule that over-stimulation paralyzes functional activity. That such an event may occur in regard to the protective reaction of the leucocytes is indicated by the fact that, in the case of horses used for the production of antidiphtheritic serum, if too large a dose of toxine or too frequent or long-continued injections are given, the cells cease to respond in the formation of antitoxine, and cannot resume their specific activity until after a long rest. The negative phase which occurs after tuberculin injections is probably something in the nature of a result of temporary over-stimulation.

Taking it altogether it would appear, with the knowledge at present available, that in those diseases (such as tuberculosis) in which the bacteria produce endotoxines and which are, for a time at least, localized, injections of toxines may be useful in prophylaxis—either in guarding against possible infection from without or against auto-infection from the disease area—but are of little use in the actual cure of the disease. For cure we want excess of antibodies within the area of the disease.

Whilst, therefore, I am profoundly sensible of the valuable work performed by Sir A. E. Wright in the discovery of opsonins and in the application of the opsonic index to the measurement of the resisting power of the individual to tuberculosis and other bacterial diseases, I am still unconvinced of the wisdom of attempting to cure pulmonary tuberculosis by the introduction into the body of a further supply of tuberculous toxine. The procedure is in my opinion too risky with our present incomplete knowledge of the details connected with the formation of antibodies, and the conditions which regulate the specific protective reaction of the leucocytes. Much remains to be done in the investigation of these processes, and this field of research promises most valuable results.

I am ready to admit that tuberculin may be a valuable adjunct to other treatment in surgical tuberculosis, and possibly in tuberculosis of internal organs other than the lungs, but it is inapplicable to the treatment of pulmonary tuberculosis. I have had, quite recently, three cases, in which, with all precautions which Wright has elaborated, tuberculin injections appeared to light up quiescent mischief in the lungs. It may be that tuberculin may be useful in those cases where, after progress has been made towards recovery, there is a check, and the patient remains in the same condition without making any further progress. In such case one or two small injections of tuberculin might result in restarting the curative process.

I have purposely limited my criticism to the case of tuberculosis, and particularly to pulmonary tuberculosis. The widespread prevalence of consumption makes every one look anxiously for the announcement of the cure which the public confidently expects. I am afraid we have not the cure for consumption in tuberculin, even

when regulated by watching the opsonic index. The value of direct immunization in certain other diseases has already been abundantly proved, and the value of the determination of the opsonic index as a guide to dosage and as a measure of progress in treatment has been clearly demonstrated. It seems possible that we are almost within measurable distance of a satisfactory specific treatment for tuberculosis, and the work of Wright has undoubtedly brought us a good step nearer the goal. Whether the specific treatment, when found, will be generally applicable to the cure of pulmonary tuberculosis, as well as to tuberculosis of other organs, is a matter of conjecture.

Whilst we are on the look-out for curative serums it might be worth while to see if we cannot obtain from the chief manufactories of antibodies—namely, the lymphatic glands of an infected animal—some extract containing the protective substances. Dr. Paterson of Glasgow has made some clinical observations in this direction in the case of tuberculosis.⁸

Though I am not sanguine as to the probability of curing pulmonary tuberculosis by either direct or indirect immunization, I think it quite possible that prophylactic immunization might be accomplished. Seeing the tremendous incidence and mortality of tuberculous diseases it would seem that "vaccination" against tuberculosis would be quite as justifiable and quite as useful as vaccination against small-pox.

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A CONTRIBUTION TO THE VALUE OF COMPLETE VOCAL REST AS AN AID TO RECOVERY FROM LARYNGEAL TUBERCULOSIS AND ALLIED CON- DITIONS DURING SANATORIUM TREATMENT.

By H. G. FELKIN, M.D.LOND.,
PHYSICIAN AT THE LINFORD SANATORIUM, NEW FOREST.

FROM the experience gained by Dr. R. Mander Smyth and myself, at Linford, I should like to add my testimony to the value of complete rest as a powerful aid to recovery from laryngeal tuberculosis during sanatorium treatment.

It has struck me as suggestive that people who have used their voice a great deal, as in singing for instance, are, when they do get pulmonary tuberculosis, more prone to develop laryngeal tuberculosis than others. Vocal rest is but a common-sense application of Hilton's principle,—rest for a diseased or injured part. A tuberculous joint is given absolute rest for many months by fixing not only itself but also the joints above and below it, and, aided by general hygienic measures, recovery takes place in many cases. The principle is true for the tuberculous larynx also, but unfortunately we cannot give it the same measure of rest as a joint. Still, much may be done, and I find the simile just used useful in explaining the great importance of complete vocal rest to patients. The rest must be complete, even whispering should not be indulged in. All unnecessary coughing must be suppressed. The laryngeal movements associated with "clearing the throat," a constant habit with some patients, must as far as possible be done away with. The nearer the disease approaches the cords, arytenoids, or arytenoid fold, the greater is the importance of laryngeal rest. It has been said that no fool will ever get cured of pulmonary tuberculosis. This statement is even truer of laryngeal tubercle. I have never yet known a patient refuse to carry out this treatment when once the simple principle underlying it had been grasped. A hint to other patients will make them helpful, and not an additional difficulty to the sufferer. Nasal breathing should be encouraged as a habit, because it is a further safeguard against useless coughing. In febrile cases the isolation in bed in their own room almost ensures silence. When the patient finds, as is generally the case, that improvement is

taking place, this acts in itself as a powerful incentive to perseverance. Most of our patients have used either a small notebook and pencil or a small slate for communicating with others; some few have learnt to talk on their fingers with their special friends. I have seen many cases of slight and moderate laryngeal catarrh associated with pulmonary tuberculosis clear up after a short period of a few weeks' more or less complete vocal rest; but these cases are common and not worth recording. One case of failure may here be mentioned, that of a lady who developed a severe tuberculous laryngitis under observation, involving great swelling and ulceration of both ventricular bands, and in which complete silence could not be enforced, though the necessity was strongly impressed upon her from the very commencement of the disease, and in which a continuous harassing, and uncontrollable cough frustrated all efforts of obtaining even approximately laryngeal rest. She did badly, but the ulceration improved under vigorous lactic acid treatment.

Of the following illustrations, Group I comprises the histories up to date of 4 cases recorded in Sir Felix Semon's paper in the *BRITISH MEDICAL JOURNAL* of December 8th, 1906, and which have been under the care of Dr. R. Mander Smyth and myself.

Group II consists of 3 cases of undoubted laryngeal tubercle and of 4 of severe and obstinate catarrh associated with pulmonary tuberculosis.

Case I (Mrs. N.) is, with the exception of Mrs. C. (Group I), the severest case of laryngeal disease associated with advanced chest disease in which I have seen great improvement without any local treatment. In Case II (Mrs. M.) a considerable ulcer healed rapidly and completely in a way it would not, I think, have done with lactic acid only.

GROUP I.

Mrs. C. returned to Linford on November 6th, 1906, her larynx being in the condition described in Sir Felix Semon's paper. In spite of the attack of pleurisy and hæmoptysis there was no material alteration in the state of the lungs. Her temperature was normal. She was treated with tuberculin. Strict silence was again maintained, and the only local laryngeal treatment consisted of an insufflation of a menthol and boracic powder three times a day. She complained a good deal of an uncomfortable "swollen" feeling in the larynx. On January 9th, 1907, there was distinctly less swelling over the arytenoids, but their inner aspect was still reddened. The cords and the rest of the larynx appeared normal. On February 27th the left arytenoid was very little swollen or reddened. The swelling on the arytenoid fold was smaller, and the right arytenoid was still swollen though less reddened. She left on March 18th, 1907, having gained 5 lb. in weight. The uncomfortable sensation in the larynx was very slight and only occasional, and the swellings of the arytenoids and over the arytenoid fold had almost completely subsided. The sputum was very scanty and contained no tubercle bacilli.

Miss S. returned to Linford for the winter on October 5th, 1906, in good general health and state of nutrition. The laryngeal scars were quite sound and the voice normal. About once in ten days she brought up a small piece of sputum the size of a small pea, which still contained tubercle bacilli. There were a few post-tussive crepitations over the left upper lobe. The temperature was normal and remained so. She used her voice very freely. She left on May 4th, 1907, in good general health. The sputum and physical signs in the lungs continued as above described. The scars in the larynx became quite inconspicuous. This was confirmed shortly after her departure by Sir Felix Semon, who even allowed her to cautiously begin singing again.

Miss W. returned to Linford on October 29th, 1906. The larynx was in the condition last described in Sir Felix Semon's paper. She was allowed to use her voice fairly freely. She left again on February 13th, 1907, the larynx remaining absolutely quiescent though the state of her lungs did not materially improve and was not so satisfactory.

Mr. W. I had an opportunity of seeing this patient three weeks ago. He was in bed after a sharp attack of hæmoptysis. He had not been in good health for some time and had lost about a stone in weight. He complained of some laryngeal pain, but the only abnormality discoverable in the larynx was a moderate degree of general congestion.

GROUP II.

Mrs. N., aged 31. She arrived at Linford on March 4th, 1903. She had a small hæmoptysis at the age of 18, but otherwise remained well until December, 1899, after the birth of a child. Since then she had suffered with cough, expectoration, night-sweats, and wasting. In the spring of 1901 she had an attack of left-sided dry pleurisy, which kept her in bed for three weeks. On her arrival she was found to have extensive tuberculous disease of both the left upper and lower lobes and slighter disease of the right apex and apex of the right lower lobe. There was a history of hoarseness, dysphagia, dis-