THE DEFENSIVE ARRANGEMENTS OF THE BODY AS ILLUSTRATED BY THE … INCIDENCE OF DISEASE IN CHILDREN AND ADULTS.

The Wightman Lecture for 1908

By SIR WATSON CHEYNE, BT., C.B., F.R.S., Senior Surgeon at King's College Hospital; Consulting Surgeon, Paddington Green .. Children's Hospital.

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THE DEFENSIVE ARRANGEMENTS OF THE BODY AS ILLUSTRATED BY THE INCIDENCE OF DISEASE IN CHILDREN AND ADULTS

Gentlemen: The choice of a subject for the present lecture has been a matter of very great difficulty, and if has not been a very fortunate one I must crave your kind indulgence. It seems to me that the object of lectures such as these is best attained by making an attempt to present a wide view of some general subject and one suggestive of future research rather than to discuss some more limited matter which would be better suited for a paper at an ordinary meeting of the Society. Hence it was among the former class of topics that my choice lay, and it has occurred to me that the subject of the relative resisting power of children and adults against infective diseases was well worth special study.

In dealing with diseases of children and adults one is often struck by the fact that marked variations occur at various ages; indeed, it is the existence of these variations which justifies a partial separation of children's diseases from those of adults, and the establishment of separate children's hospitals, or, at any rate, of wards in general hospitals set apart from the treatment of children. In the present lecture I shall speak only of diseases which are due to the entrance of parasitic organisms from without with special reference to the points of difference in children and adults. I am not able to explain these differences satisfactorily – I can only indicate some of the points which arise in the hope that some members of this Society who have more time and more ability than I have will turn their attention to the study of these matters. I believe that the successful study of the differences in the resisting power of children to infective diseases as compared with adults will give the key to much of the obscurity and difficulty which still surround the questions of infection, protection and immunity.

In looking into this subject we find that there are some diseases which practically only occur during childhood, and vice versa that there are certain diseases common in adult life which hardly ever affect children. Again, we find that there are many infective diseases which attack both adults and children, but the young are more especially susceptible to some, while their elders are more susceptible to others. Or, again, we find that some diseases are more virulent in children than in adults, and vice versa. Perhaps the most striking fact of all, and the one to which I wish especially to draw your attention, is that in diseases which are common to both children and adults the organs and tissues which are attacked by the virus may differ markedly according to the age of the patient.

That such differences in the incidence of disease in children and adults are very common is a point which hardly requires any elaboration. The *exanthemata*, for instance, are very often spoken of as children's ailments, and some explain the fact that they are most frequent in children by saying that practically all individuals are highly susceptible to them, and being widely spread, no individual can live long in the world without being exposed to infection. This may be in part true, but I can hardly accept it as a complete explanation of the facts; I cannot but think that, quite irrespective of opportunities of infection, the susceptibility of the individual varies according to age. Even in the case of children, the exanthemata differ among themselves as to the age when they most frequently occur; for example, measles is not uncommon during the first year of life, and something like 90 per cent. of the cases

occur in children under 5 years of age, while scarlet fever rarely occurs in infants, although patients suffering from it may be present in the house or even in the same room, and the favourite age for scarlet fever is from 3 to 10 years. Then, again, chickenpox occurs at a somewhat later period than scarlet fever; it is not so universally distributed, and it very rarely affects adults.

To take an organism whose life-history is known, we have a very good example of varying susceptibility at different ages in the case of the *pneumococcus*. This organism attacks the body more readily in childhood than in adult life, or as I would prefer to put it, the resisting power of the human body to the pneumococcus is apparently lower in children than in adults; thus it seems to be the fact that pneumococcal pneumonia is more common in children under 5 years of age than during any other quinquennial period. One of the most interesting points from a surgical point of view is the relation of the pneumococcus to pleurisy and empyema. The organisms which are most commonly at work in setting up these conditions are the pneumococcus, the *Streptococcus pyogenes* and the tubercle bacillus; other organisms, such as *Bacillus coli*, staphylococcus, &c., are quite rare. Now, the relative frequency of these organisms in cases of empyema differs very markedly in children and adults. Thus, in children, over 60 per cent. of the cases of empyema are due to the pneumococcus, about 15 per cent. to the streptococcus and about 7 per cent. to the tubercle bacillus. In adults, on the other hand, the proportions are: pneumococcus, 25 per cent; streptococcus, 41 per cent.; and tubercle bacillus 18 per cent. Thus, the pneumococcus is the most common case of emypema [sic] in children and the streptococcus in adults. In children, pneumonia is present in cases of pleurisy in from 25 5o 50 per cent; in adults, it is present in only about 20 per cent. Further, pleurisy more often becomes purulent in children than in adults; indeed, empyema after pleurisy is about four or five times more common in the former than in the latter.

I think there can be little doubt that the meaning of these facts is that children have less resisting power against the invasion of the pneumococcus than is the case of adults, and this view is strengthened by the fact that we more often meet with pneumococcal invasion of other parts of the body than the lungs and pleura in children than in adults. Thus we find that while pneumococcal peritonitis occurs at all ages it is much more frequent in children, being most common between three and ten years of age. Similarly, pneumococcal disease of joints is also most common in children, and the general invasion of the body by the pneumococcus is a very striking feature in early childhood and is most marked in infants, where we may have a regular pneumococcal septicæmia.

I need not give further examples of the general proposition that difference do occur in the incidence of various infective diseases in children and adults respectively, but may at once go on to the consideration of further points in connection with such differences. The question of infection is a very complex matter, and a variety of factors come into play in connection with it. On the one hand, we have the *invading parasites*, and on the other the *defensive arrangements* of the body against this invasion. I need not here go into the questions which relate to the parasites, their virulence, their habitat in the body, their habitat outside the body, the varying ease with which they gain access to the body, and so on, seeing that these points are the same whether the individual attacked is young or old. Passing, however, to the other partner in the infective process, namely, the animal body, we find that there are a

variety of conditions which are necessary before the invading organisms can obtain a foothold in the body.

The first line of defence of the body resides in all probability in the epithelial tissues which oppose the entrance of infective agents into the body, and differences in the amount of resistance which they oppose to the entrance of organisms exist at different periods of life.

It is not as yet possible to define the exact meaning of the condition of the epithelium which enables it to oppose invasion. It clearly must be a local power residing in the epithelial cells themselves, or in the fixed cells on which they are situated, rather than any general condition such as the presence of opsonins in the blood, &c. It is interesting to note, as shown long ago by Lister, that where the epithelium lining a canal, the sides of which are normally in contact, is intact and healthy, bacteria cannot spread along that canal. This is true in the case of many ducts, such as the urethra, the mammary ducts, the salivary ducts, &c., and Lister used to point to this as a proof of the vital power of the tissues in preventing the growth of bacteria.

A very good example of variation in the defensive power of epithelium according to age is furnished by the behaviour of the *gonococcus*, and two points occur in connection with this organism in children. In the first place, there are reasons for believing that the susceptibility of children to the invasion of the gonococcus is greater than in adults; and in the second place, the organism attacks epithelial tissues in children, which are more or less immune in adults. The very mode in which infection occurs in the two cases seems to imply a diminished resisting power on the part of children, for in them infection is usually accidental, being conveyed by dirty sponges, soiled linen, &c. No doubt the anatomical development of the parts such as the vulva, as age advances, may render accidental infection less easy in adults than in children; but still it occurs more readily in the latter than this would account for. The incubation period in children is also apparently shorter than in adults. The disease as it occurs in young people after infection is usually more severe than in adults, and there are various observations which seem to show that discharges which are no longer capable of infecting the mucous membranes in adults are virulent for those of children. The greater readiness with which the conjunctiva becomes infected in children may also point to increased susceptibility to the gonococcus, though possibly the fact that in infants the conjuctiva is only one layer of cells thick, may have something to do with the greater susceptibility. The special interest, however, centres in the location of the disease in children and adults respectively – namely, in the fact that the vaginal mucous membrane is more often and more violently attacked by the gonococcus than in adults. In adults, as a matter of fact, the disease is usually located in the cervix uteri or in the mucous membrane of the urethra, while involvement of the vaginal mucous membrane is relatively rare and slight. Some, indeed, altogether deny the susceptibility of the vaginal mucous membrane to the gonococcus in adults, and hold that when it is diseased it is only affected by a sort of desquamative catarrh caused by the maceration of the mucous membrane from the passage of the pus over it. While the vaginal mucous membrane in children is thus highly susceptible to the gonococcus, it is curious that other complications caused by this organism are not so common nor so severe in children as in adults. No doubt gonococcal peritonitis does occur, and it is quite likely that the so-called spontaneous peritonitis in young girls is often of gonococcal origin. Gonococcal cystitis is also not uncommon, but gonococcal

infection of joints is rarer than in adults. It most commonly affects only one joint, usually the knee; hydarthrosis is not observed, ankylosis is very rare, and on the whole the course of gonococcal joint troubles is more benign and not so chronic as in adults.

Another example of the relation of organisms to the first line of defence is furnished by the behaviour of the pyogenic organisms in the skin. *Multiple abscesses of the skin* and subcutaneous tissues are quite common in infants. Impetigo is also common, but boils rarely occur. The reverse is the case in adults, where multiple abscesses of the skin are quite uncommon, their place being taken by boils. What the explanation of the difference is is not quite clear, but it is quite possible that in this instance it is in the main a question of differences in the anatomical structure of the skin rather than of general defensive arrangements. Thus, in children, the desquamation of the skin is more active and there is also incomplete development of the corneous layer of the epidermis in various places; in fact, the epidermis in children is very thin and extremely fragile and it desquamates readily, leaving the rete mucosum exposed. The papillary layer of the skin is also very rich in blood-vessels and reacts readily to all irritations.

Having overcome the first line of defence, the parasites either produce a local disease at that part, as we have seen in the case of the gonococcus, or else (and this happens in the majority of cases) they pass on into the lymph or blood-stream and are carried to various parts of the body. In this latter case, having passed the epithelial line of defence, they then find themselves in closed tubes lined with endothelium. Apparently, some forms of bacteria, having reached the circulating blood, can multiply in it and set up disease, but the great majority, and probably to a greater or lesser extent all, have to find a local resting place; if they fail to do so they quickly die out. We may imagine the bacteria being carried along in the circulation through the various tissues of the body, investigating these tissues as they pass through them till at last they find somewhere or other, in the endothelial lining of the vessels, conditions which are favourable for their growth or penetration; and, therefore, we may assume the existence of a second defensive arrangement – namely, the endothelium. Having found a weak spot in the endothelial lining, they grow there and produce disease or else they pass through the wall of the vessel as they did through the epithelium, and multiply in the tissues outside. We have evidence that in a good many cases the parasites grow in the endothelial lining of the vessels. In syphilis, for example, endarteritis is the chief lesion, and is probably due to localization of the spirochæta in the inner coat of the small vessels. In the case of tubercle, also, I pointed out some years ago, in my essay for the Astley Cooper prize, that many tubercles are formed in the first instance in the interior of the blood-vessels possibly by proliferation of the endothelium, and in some specimens one can see tubercles in all stages clearly illustrating this point.

What the local predisposition on the part of the endothelium and the tissues signifies, it is difficult to say. To some slight extent it may have to do with the *general* trophic condition of the parts, as influenced by the action of the nerves. In connection with this point, I may refer to the interesting observations which have been made by Mr. Cheatle on the sites of development of epithelial cancer and its mode of spread, in which he produces some very remarkable examples of the spread of cancer along certain definite nerve areas, avoiding neighbouring area supplied by other nerves. To

a considerable extent it may be a question of *pabulum*. That the nature of the pabulum is of very great importance in the artificial cultivation of micro-organisms is, of course, well-known. We know, for example, that it is not easy to cultivate the tubercle bacillus outside the body, we know that in cultivating the gonococcus it is necessary to have a little human blood on the surface of the cultivating medium to enable the growth the start; and we know that up to the present investigators have not been able to find a soil and external conditions which are suitable for the growth of various other infective organisms, such as those of leprosy, &c. It is, therefore, not at all unlikely that in the living body the question of suitable pabulum may have a good deal to do with the localization and growth of the organism.

An example which seems to point in this direction is that of ringworm of the scalp. This disease may affect children of all ages, but is rarely noticed before three, or after fourteen, years of age; it never appears after the age of fifteen, and adults may mix freely with children suffering with ringworm of the scalp without being attacked by the disease; while on the other hand it is extremely infectious for children, and will run through a school very quickly. The disease, if left to itself, disappears spontaneously at puberty – fresh and healthy hairs growing on the affected site. This is a very curious case, and it seems difficult to frame a reasonable explanation. The fungus penetrates into the hairs close to the roots, but it evidently does not destroy the hair bulbs, otherwise the hairs would not grow again. It is, therefore, growing in what is practically dead tissue, or at the best in tissue of extremely low vitality; and the curious thing is that though it grows readily in this tissue in children, it cannot grow in what is to all appearances the same material in persons over fifteen years of age. Is it that there is a difference in the chemical composition of the hairs in adults and children, and is it only in children that they provide suitable food for the fungus. Or, is it that the fungus penetrates into tissue which still retains a certain amount of vitality; and are there more vitality and more resisting power in it in adults than in children? Whatever be the explanation, I think that this question of the suitability or unsuitability of the food which the parasite finds in the part which it invades, must not be overlooked in considering the various factors which go to make up the defensive arrangements of the body.

Another example which may be mentioned in this connection is that of the common *threadworm*, which is only, or at any rate, very much more often, found in children than in adults. Threadworms are very common in the large intestine of children, and they probably enter along with the food or drink. They occur in children at an age when their food is practically the same as adults, and yet threadworms are essentially a disease of childhood. May not this again be simply a question of pabulum? Is there a difference in the contents of the large intestine in children and adults, consisting in the presence of substances suitable for the existence of these worms in the former, such substances disappearing as the individual reaches adult life? Or is it that there is something in the intestinal secretions of adults which is inimical to the growth of the threadworm and which is absent in children? This might be an interesting physiological problem to work out. I can hardly think that in this case, at any rate, it can be a question of tissue resistance; for the worms grow in the fæces and can hardly be affected by the living cells lining the canal.

In this connection, also, I may refer to an interesting point – viz., that bacteria of the same species may acquire a special appetite, so to speak, for certain tissues. For

example, while we look on the Staphylococcus pyogenes as an organism which may cause suppuration indifferently in any suitable tissue in which it may happen to find a proper resting-place, we find that in certain cases where fresh developments of these organisms take place in the same individual, they are apt to occur in connection with similar tissues. Thus, I have repeatedly seen cases of staphylococcal osteo-myelitis in which fresh outbreaks of osteo-myelitis have occurred in several bones in succession without the occurrence of suppuration in other tissues of the body, as if the organisms which had settled in the bone in the first instance had acquired an appetite for bone, and when carried to other parts of the body again, selected the growing ends of the bone for their development. This is, perhaps, still better seen in tubercle, where in cases of tuberculous disease of the bone we not uncommonly find that if fresh tuberculous disease occurs it is in other bones, and the tubercle may remain limited to bone for a long time. This is often the case, for example, in infants with tuberculous osteo-myelitis of the small bones of the hands and feet. Again, we have the tubercle bacilli in some cases showing a special tendency to grow in the lymphatic glands, and not for a time spreading in other tissues, or in other cases growing in the skin and giving rise to lupus without leading to tuberculous disease elsewhere.

Stress had also been laid by some on the anatomical arrangements of the various parts as favouring the deposit of micro-organisms in certain situations. For example, in the case of osteo-myelitis, the slower circulation at the epiphysial line may permit the deposit of organisms at that part, and thus account for the localization in cases of this disease; indeed, it has been found experimentally that pigment granules injected into the blood are deposited in these situations. We cannot, however, accept this as the only, or indeed as a particularly important, factor, for many things point to something much more far-reaching than a mechanical deposition of bacteria. Thus the incidence of disease in various bones differs according to age and also according to sex. For example, osteo-myelitis is most common between the ages of twelve and eighteen, and at that age it is more frequent in the lower extremity than in the upper, and also more frequent in boys than in girls. On the other hand, the disease may attack children at a much earlier period of life, even below two years of age. In that case the upper extremity is affected nearly as often as the lower; the limitation of the disease in the first instance to the epiphysial line is not so marked, and, indeed, the lesion may occur in the epiphysis itself, and boys and girls are affected pretty equally. The anatomical arrangement of the part may possibly exercise some influence in favouring infection and determining the spread of the disease, but it is evidently a very minor factor.

It seems to me, then, that the localization of the disease is in the main a vital question, which may be summed up under the term *"local predisposition."* As showing the complexity of this subject, it may be pointed out that similar tissues in different parts of the body do not show the same susceptibility. Thus we know that the gonococcus seldom affects any mucous membranes except those of the urethra and the conjunctiva; and we shall presently see how tissues of various joints and bones in the body react differently to the tubercle bacillus at different ages. The same is the case if we take more general diseases. Thus, in the case of plague, Dr. W.J. Simpson points out that bubonic plague especially attacks the lymphatic glands in the groin and the axilla, especially in the groin, no matter whether the infection has occurred by punctures of the surface or in some less-defined manner. We must, therefore, assume that the lymphatic glands in the groin differ is some way or other in their vital relations to these particular organisms from other lymphatic tissues in the body. To

take another example – in acute tuberculosis, although we must assume that there is a general flooding of the blood-stream with tubercle bacilli, and that the circulating blood carries organisms all over the body, we nevertheless find that the bacilli are not deposited and grow anywhere indifferently but that they select certain organs and tissues. For example, they are seldom found in the muscles and cellular tissues. In the case of infants who die from tuberculosis during the first four months of life, it is found that the disease is practically always general, but the parts of the body in which the tubercles are deposited vary very considerably. Thus, in post-mortem examinations of these infants, tubercles are found in the lungs in all cases; in the bronchial glands, in 99 per cent. of the cases; in the liver, 88 per cent., in the spleen, in 86 per cent.; in the brain, in 24 per cent, and so on. And again, taking the brain for example, they are not equally deposited over the whole brain but prefer to locate themselves along the vessels at the base.

The local predisposition varies to a very marked extent with the age of the patient, the parts affected differing at different periods of life. Perhaps the best example of these variations is furnished by the incidence of tuberculous diseases of the bones and joints at various ages. In the great majority of cases of tuberculous disease, where the bacilli which escape into the blood-stream are few in number, a very close selection is made, and only one, or at most a few, local deposits occur, and that apparently only under the most favourable conditions. What these conditions are which favour the deposit of tubercle bacilli in a particular part we really do not know; but, as has just been said, they vary with age and to some extent sex, and also with a variety of so-called predisposing causes – such as injury or chronic inflammation.

Some years ago, I collected a large number of cases of diseases of bones and joints in adults and children which had been treated in hospital, and the following remarks are founded on these statistics. In the first instance, taking a general view of the relative frequency of disease in bones and joints at different ages, I would direct attention to the accompanying table, which gives the percentage frequency of the total cases of disease of bones and joints in my list in each quinquennial period up to the age of forty years.

TABLE I – *Percentage Frequency of Disease of Bones and Joints in each Qinquennial Period, up to the Age of 40 years.*

Age periods – years	Percentage of total number of cases	Age periods – years	Percentage of total number of cases
1 to 5 …	23.3	21 to 25 …	8.5
6 to 10 …	16.0	26 to 30 …	8.8
11 to 15 …	14.8	31 to 35 …	4.0
16 to 20 …	15.0	36 to 40 …	3.0

This table indicates clearly the great importance of age in relation to the occurrence of these diseases, but it does not accurately represent the facts of the case. Thus, it may quite well be that a greater number of cases occur during the first five years of life, because a greater number of persons are alive at that age than during any other quinquennial period. Conversely, for the same reason, it may turn out that the disease is much more frequent than appears to be the case during the later quninquennial periods, owing to the smaller number of persons alive at that time. Investigations of this kind have been made with regard to phthisis, and have led to the surprising result that in Copenhagen, Sweden, and various German cities – with regard to which calculations have been made – the danger of phthisis in any given individual constantly increases with advancing age, and that in advanced life a larger proportion of the individuals alive at that age die from phthisis than at the period of life in which it has been supposed to be most common.

TABLE II. – *Ratio per 1,000 of Cases of Disease of the Seven Larger Joints in each Quinquennial Period up to the Age of 45 years.*

Age-period – years	Apparent frequency	Real frequency
1 to 5	232	167
6 to 10	153	134
11 to 15	150	145
16 to 20	153	164
21 to 25	85	98
26 to 30	88	120
31 to 35	41	60
36 to 40	30	48
41 to 45	20	42

Employing the German statistics of the proportion of persons per 1,000 alive at various ages, I have calculated the real frequency of the disease in my cases, and in the foregoing table we have the ratio per 1,000 of my cases of disease of the seven larger joints, beginning in each quinquennial period. In the second column, I give the apparent frequency of the cases without relation to the number of persons alive at the different ages, and in the third column, the real frequency as calculated by the above method. I only give the results up to forty-five years of age. (See Table II.)

From this table it will be seen broadly that the real frequency of these diseases is actually greater in advanced life than would appear from the ordinary statistics, but is still a good deal less than in youth. In my list, the disease commences most frequently between one and five years of age; it then declines and rises again between fifteen and twenty years; it subsequently steadily declines, with the exception of slight rises between thirty-five and forty years, and forty-five and fifty years. The accuracy of the last numbers, which are not given here, is, however, very doubtful, because the cases in my list which commenced at those ages are quite few in number. Great differences also exist as to the period of life at which the disease commences in the different joints and bones, as is evident from the following table, in which I have indicated the

percentage proportion of the cases of disease in each of the seven larger joints, commencing in each decade: -

Table III. – *Percentage Proportion of Cases of Disease of each of the Seven Larger Joints in each of Five Decades*

Joints	Decades				
	I	II	III	IV	V
Hip	30.2	29.3	4.8	-	12.5
Knee	29.5	22.8	18.2	36.6	6.2
Ankle	5.4	5.9	3.6	3.3	12.5
Tarsus	4.6	5.9	8.4	3.3	18.7
Shoulder	-	1.6	4.8	-	-
Elbow	6.7	9.2	6.0	13.3	18.7
Wrist	0.6	8.4	15.8	13.3	6.2

Thus, reading the table from above downwards, we see that of the total cases of tuberculous bone and joint disease which commenced during the first decade, 30.2 per cent. were cases of hip-joint disease, 29.5 per cent. were cases of knee-joint disease, and so on. Reading the table from side to side, we see the frequency with which disease of each part commences in each decade; thus, hip-joint disease commences most often during the first decade, and its frequency diminishes very rapidly. The knee-joint is also very frequently attacked during the first decade, but the fall in its frequency is by no means so rapid, and so on.

Not only does the resisting power of the body vary in the same individual at different ages, but it is very interesting to note that it often varies very considerably in the two sexes. Thus, speaking of tuberculous diseases of bones and joints, I find that of the patients on my list 65 per cent. were males, and only 35 per cent. are females. Indeed, most forms of surgical tuberculosis are more frequent in boys than in girls. The following table[1] gives the percentage relations of males and females (hospital in-patients) in regard to diseases of the seven larger joints, and it will be noticed that not only are males more frequently affected than females, but that the proportion differs in different joints. And not only are there differences in the incidence of disease in the two sexes, but the disease in the female seems to be as a rule more benign than in the male. That is a very interesting matter, which, however, I have no time to discuss here. I may also remark that while this is the case with regard to diseases of joints, it does not necessarily hold good with regard to some other forms of tuberculous disease. Thus, tuberculous peritonitis is almost equally frequent in the two sexes, while lupus is much more common in females than in males.

[1]I would not, however, press the actual percentages which are mentioned in this table, because in some of them, especially in the case of the shoulder, the number of patients was too small to be of value.

TABLE IV. – *Percentage Relations of Males and Females in each Joint.*

	Hip	Knee	Ankle	Tarsus	Shoulder	Elbow	Wrist
Males	59.7	57.6	81.9	85.8	50	74.3	75.9
Females	40.3	42.4	18.1	14.2	50	25.7	24.1

The predisposition and resisting power of the body, both local and general, to parasitic invasion vary very markedly under a variety of circumstances and are often very sensitive to external conditions. Even the seasons of the year apparently have their influence on the resisting power of the body. For example, erysipelas is more frequent at certain periods of the year than at others, especially during February and November, and lupus is said to improve in autumn and to become worse in spring.

One of the most important causes which influence the local predisposition of a part is injury. In the case of the epithelial tissues injury is naturally of great importance in connection with their defensive action. If there is a solution of continuity in these tissues, parasites may enter through a breach of the surface without being subjected to the action of the epithelium at all. On the other hand, without actually destroying the epithelium, the injury may so depress the vitality of the cells that they can no longer successfully resist the parasitic invasion.

A very good example of the effect of injury is furnished by the history of tuberculous disease of bones and joints, and the facts are of considerable interest. As a rule, where a case of joint disease is referred to as an injury, the history given is usually that of some slight injury – such as a strain or slight blow; indeed, it is noteworthy that after severe injuries in tuberculous subjects, such as fractures or amputations, tuberculous disease does not occur at the seat of injury. Thus, I can recall more than one instance of patients suffering from tuberculous joint disease who sustained fractures – in one case of the shaft of a bone, the epiphysis of which was already diseased, where the fractured ends have reunited without the development of any tuberculous disease at the seat of injury. And as regards amputation, unless the operation is carried out through parts which are actually diseased, one does not expect to have a tuberculous stump as a result, however many tuberculous lesions the patient may suffer from. We also not uncommonly notice that after tuberculous joint disease has become quiescent, or even apparently got well, it may recur as the result of a slight injury.

A further point which is worth mentioning is that injury to some joints seems more likely to be followed by tuberculous disease than injury to other joints. This fact is in accordance with the view which the above tables must lead us to assume – that the different joints vary in their predisposition to tuberculosis disease, and that consequently injury is more likely to have an effect in determining its occurrence in those joints which are naturally the most predisposed.

Lastly, I may mention that it seems from my statistics, with which I need not trouble you here, as if injury were not only an active agent in the production of these diseases, but also determined a graver form. In my list, the cases in which injury was given as a cause were on the whole more serious than those where no cause was assigned,

whether we judge by the occurrence of suppuration, the results as regards complete recovery, or the severity of the treatment required for the cure.

One very obvious way in which injury may act in determining the occurrence and localization of infective diseases is by leading to extravasation of blood, and if bacilli happen to be floating in the blood, to their consequent deposit in the part, in this way breaking down the second line of defence – namely, the endothelium – just as the first line of defence may be broken down. Apart from actual rupture of vessels and extravasation of blood, injury may favour the deposit of bacilli in the part, in that it leads to changes similar to those noticed in the early stages of inflammation. These changes involve, I believe, in the first instance, a diminution in the resisting power of the tissues. I fancy that at the present time such a view of the result of the early stage of inflammation would hardly be assented to, because the leucocytosis which accompanies it is looked on as a most important part of the protective arrangements of the body. I would, however, refer to Lister's early observations on inflammation, especially on the effects of inflammation on the activity of the pigment cells of the frog, to show what a paralysing effect irritation has in the first instance on the functions of the tissue cells of the affected part; and my belief is that the essential resisting power of a part as regards local infection lies in the tissue cells rather than in the adventitious leucocytes which come into it subsequently; and this may explain the greater severity of the disease after injury. I have formerly pointed out that where an extra large number of infective agents enters a part, a more severe form of disease always results; and it must be remembered that this question of dosage of infective agents is, of course, relative to the resisting power of the part. Where, therefore, a similar quantity of bacteria has entered two parts – one of which has been rendered less resistant as the result of injury – this dose will act in the latter case in the same way as if a large dose had been administered under ordinary circumstances.

Resisting power is also influenced by a variety of conditions apart from those already mentioned, and these are often spoken of as predisposing causes of disease. There seems no reason to doubt that exposure to cold especially affecting a sensitive mucous membrane is a potent factor in permitting the entrance of pathogenic organisms, and very probably has a great deal to do with the penetration of such organisms as the pneumococcus into the body, especially into the lungs. Bad hygiene, bad food, starvation, alcoholism, &c., are also important agents in lowering the resisting power of the body to disease, and the same is frequently seen as the result of other illnesses, such as influenza, measles, chicken-pox, &c. To take the case of multiple abscesses in the skin in childhood, to which we have already referred, we find that they often follow acute and chronic illnesses. Thus, they are frequent during convalescence from infective diseases, such as typhoid fever, pneumonia, influenza, &c., and in the course of measles, scarlet-fever, and small-pox, abcesses and even gangrene of the skin frequently occur. They are also quite common in tuberculous children. Presumably, therefore, these diseases lower the resistance of the body to the staphylococcus, and yet, curiously enough, taking tuberculosis for example, I find no evidence that the opsonic index to staphylococcus is as a rule seriously lowered in cases of tuberculosis.

In connection with this question of variation in the resisting power at different ages, a very interesting point arises which is worth mentioning here. One would naturally assume that if one individual is more susceptible than another to a disease, he would also be affected by that disease in a more severe form – and no doubt this is true in a

very considerable number of cases – but there are a number of very remarkable exceptions. In the case of the exanthemata, although I cannot speak with authority, I have seen it stated, and I have been brought up in the belief, that if an adult is attacked the disease is more likely to assume a severe type than in the case of a child. And yet we have already assumed that an adult is less susceptible than a child. In the case of pneumococcal invasion of the lungs, although the largest number of cases occur below twenty years of age and, therefore, presumably during the most susceptible period, the greatest mortality takes place in patients above twenty years of age. In the case of tubercle we find also that while it is most common in young people the disease is most obstinate and less amenable to treatment in old people. And again, with regard to tubercle, while it is not common during the first year of life, when it does occur it assumes a very grave type, owing chiefly to the fact that it is very apt to become generalized, and this is also true in the case of other infections, such as pneumococcal, streptococcal, &c. We have, however, many examples in the other direction. Typhus fever, for instance, is rarer in children than in adults, but it is not so dangerous in children as in adults. Again, typhoid fever is not so common in young children as in young adults; being most frequent between twenty and thirty years of age, and quite exceptional below eight years of age. We may, therefore, assume that susceptibility to typhoid fever is small below eight years of age, that it reaches its height between twenty and thirty years of age, and again diminishes later. But the curious point is that the mortality increases as the age advances, being 11.3 per cent. in children below ten years of age, and reaching 34 per cent. in persons over fifty years of age. Other examples of both these points might be given, but the above will suffice for our purpose.

A probable explanation of these facts is somewhat difficult to formulate, but the two following points are, I think, worth taking into consideration. In the first place, I have already referred to the question of relative dosage of bacteria in speaking of injury, and it is quite possible that this point also comes into play here. Thus, while a comparative small dose will suffice to set up the disease in a susceptible individual, it requires a larger dose where the subject is less susceptible. And in accordance with the results which I obtained some years ago, the resulting disease with the larger dose in the less susceptible individual, would be more severe than that with the smaller dose in the more susceptible person. But in the second place, I would point out that it is as a rule when the less susceptible individual is over the average age, that the resulting disease is more severe; whereas this is not necessarily the case when he is under the average age – always excepting the first year of life. Hence, it is probable that another factor besides resisting-power comes into play in infective disease, and it is with the view of calling attention to this other possible factor that I have introduced the matter here. This factor may be indefinitely spoken of as *recuperative power*. It is quite probable that apart from the agents which actually take their place in the fight against the invading parasites, there are other agencies which have to do with the maintenance of the health of the body and with the restoration of strength after it has been subjected to infection; and those I should group under the term “recuperative power”. And I am inclined to think that some factor of this kind plays an important part in the recovery of patients from infective disease, quite apart from any antitoxic or anti-bacterial agencies. Leaving out the question of infective diseases, we know that as people get older they do not recover so quickly and perfectly from injury or illness as is the case in youth. To some extent, and probably to a considerable extent in old people, this has to do with the general onset of degenerative changes in the

various tissues, and perhaps more especially in connection with the blood-vessels. If I am correct in suspecting the existence of some further vital energy of this kind, its importance in treatment cannot be overlooked; and especially it warns us not to pin our faith as regards treatment to one single point, but to try to influence all the agencies which have to do with the well-being of the individual.

Time will not permit me to pursue this subject further. I could have mentioned many other facts in illustration of the points to which I have referred, but those which I have picked out seem sufficient to show the bearings of the matter, and to indicate its great interest and importance. Especially, I think, there can be no doubt of the existence of local conditions in the tissues and organs of the body which have a very important bearing on the occurrence of infection and on recovery from it. Indeed, in my opinion, the local conditions, which we have grouped together under the heading of "local resisting power", are of much more importance than any general agency which may be present in the blood-stream.

I have already indicated some points which have to be taken into consideration in connection with this question of local resisting power, but in spite of all the work that has been done, we are still in the stage of theory. One point I may refer to in connection with this matter, and that is the remarkable difference as regards leucocytosis in the new-born and in later life – taking the example of erysipelas. Erysipelas shows very marked differences in gravity at various periods of life and under various circumstances, and it is more especially grave in the case of infants. Infantile erysipelas usually appears from the tenth to the fifteenth day after birth, and generally spreads from the umbilicus. Its mortality at that age is at least 50 per cent., but the mortality steadily falls in older children. On examining the parts in infantile erysipelas the most interesting fact is observed that there is almost complete absence of local leucocytosis. In the adult, leucocytes group themselves in large numbers around and within the blood and lymphatic vessels, while in the new-born one finds the vessels dilated it is true, but this is due to the presence of masses of streptococci and not to leucocytes. Enlargement of the lymphatic glands, which also occurs in adults, may be very slight or absent in children.

On the other hand, leaving out the first year of life, there seems to be a slight increase in general leucocytosis in children under ten years of age as compared with older people in some of these infective conditions. This has been especially pointed out in cases of otitis and mastoiditis.

That the conditions summed up under the term "local resisting power" are much more important than the more general conditions seems to me to be certain, and I have mentioned quite a number of points which indicate this. I have especially referred to the varying local incidence of disease at different ages and under different conditions; and I may also mention another very striking point as showing the importance of local, as compared with general, defensive arrangements. It is this – that in some cases one finds a disease making good progress towards healing at one part of the body, while at the same time a fresh outbreak is taking place at another, Take, for example, the case of tertiary syphilitic ulcerations. One of the important diagnostic points after a tertiary ulcer has lasted for some time, is the tendency which it has to heal at one side while it spreads at the other, in this way giving rise to the serpiginous form of these ulcers. If the healing were due to general conditions in the serum, why

should it not occur all round; and why, if the resisting power has been so much improved as to lead to healing at one part, does the disease actually progress at another part in the vicinity? The same is frequently seen in the case of tuberculosis; it is not at all uncommon to find one tuberculous deposit healing or becoming quiescent, while another becomes active or a fresh one actually appears. A very good example of that is seen in tuberculosis of the epididymis, where the disease on the one side and also in the vesiculæ seminales may be steadily improving, when all of a sudden the other side becomes affected and not uncommonly runs a more virulent and rapid course than the first. I have seen exactly the same thing happen on several occasions in cases of tuberculous which had been under steady opsonin treatment for a long time – some of them over a year. This, in one case of tuberculous epididymitis which I recall, the disease in the epididymis was particularly acute in the first instance, and I advised opsonic treatment rather than operation. Ultimately, however, as the testicle became completely destroyed by suppuration, castration became necessary. Opsonic treatment was still steadily continued under the best auspices, but in spite of that, residence at the seaside, &c., the disease appeared acutely in the other epididymis, while the treatment was still going on, and I had to perform an epididymectomy without delay in order to save the other testicle. The course which the disease followed was in reality the same as if no attempt had been made to increase the general resisting power.

At the present time, it is the fashion to look on the opsonic content of the blood as the essential agent concerned in bringing about immunity and care in the case of infective diseases. This is a matter on which neither time nor knowledge permit me to enter at length. I have, however, searched the literature, inquired among investigators, and had a few observations made for me without finding any marked differences in the opsonic index to different organisms at various periods of life corresponding to the variations in the incidence of disease, and in their course at different ages; nor has any difference in the opsonic index to various infective organisms been pointed out as regards sex, and yet, as we have seen, there are noticeable variations in the incidence and severity of these diseases in the two sexes. It must, however, be pointed out that this matter of alterations in the opsonic index in connection with age, sex, &c., has not yet been worked out from the point of view taken in this lecture, and we must not, therefore, lay too much stress on our present knowledge on this point. It is a matter which it would be quite worth while looking into. The only investigations actually bearing on this point which I have come across are some described by Dr. J.H. Wells in the May number of the *Practitioner*. He has made observations on the opsonic index in infants under one year old, with the result that he finds marked differences in young babies as compared with older people. He comes to several conclusions, of which I may mention the following: -
“A low opsonic index is not diagnostic in children under one year old.” “In infants a low opsonic index is not inconsistent with health, and the child may be thriving well with a declining index.” The anti-bacterial defence in children cannot depend upon the opsonic content of the serum.” These are very important conclusions, and if found to apply to a sufficiently large number of cases, they raise the question whether the significance of the opsonic index and opsonins generally is being properly interpreted. Although infective troubles, when they do occur in infants are, as a rule, more acute than in older children – as already instanced in the case of tuberculosis, erysipelas, &c. – nevertheless, infants do not develop these infections so readily as children do after the first or second year of life – in general terms, their defensive power is

greater. But, if it is a fact that the anti-bacterial defence in infants does not depend on the opsonic content of the serum, and yet at that period their defensive powers are high, is it right to assume that at a later period of life the antibacterial defence does depend on the opsonic content of the serum? May there not be some other interpretation of the variations in the opsonic index than that which is put forward by Wright and which is being so extensively translated into practice?

I must confess that while there is much that is interesting and important in the extensive work which is at present being done on opsonins, it would be more convincing to me if the theories on this matter were less complete and simple, and if the writings were tinged with a little philosophic doubt. Unfortunately, when we come to study the results of the application of these theories to practice, they do not work out as they ought to do. In some cases good apparently does result, while in others it is an open question whether the benefit which follows would not have occurred to an equal extent without the vaccination; in may instances, however – and my experience especially concerns tubercle – one cannot convince oneself that the slightest benefit has resulted – in some, indeed, the condition seems to have become worse. Nor even in the cases where benefit has resulted is it clear that the bacteria have been completely eradicated, as one would expect if the theory were correct. I think that all we can say about these matters at present is that they are highly interesting from a scientific point of view, and that their continued study is highly desirable, but that it is very doubtful if the opsonin theory is the complete solution of the problem. For my own part, I feel satisfied that something is still wanting, and I believe that the discovery of that something will be more likely to be made in connection with the study of the local conditions of resisting power, than of the general conditions of immunity. The time has certainly not yet come when we can, with advantage to our patients, beat our knives and stethoscopes into hypodermic needles and syringes, discard all our past experience and knowledge, and transform ourselves into immunisators.