LECTURES ON SUPPURATION AND SEPTIC DISEASES.

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LECTURE III.

I MENTIONED in the last lecture that, as the result of differences in the seat of inoculation, and the anatomical arrangement of the part, there may be differences in the character of the disease produced. Virchow has long ago pointed out that the cause of a disease does not by any means determine the product of the disease, for that depends chiefly on the internal predisposition; thus the same agent acting on the cellular tissue may cause thickening of it, and, acting on the periosteum, may lead to ossification. This is probably in part the explanation of the different types of disease produced by these pyogenic organisms according as they act in the skin or in the connective tissue. I have previously mentioned the result of Bockhardt's investigations on impetigo and boil, from which it is evident that the character of the inflammation depends greatly on the point of entrance, and the seat of development of the organisms, and Garré has also come to the same conclusion.—It seems that in the case of multiple abscesses of the skin in infants, the cocci spread into the hair follicles, and sebaceous and sweat glands, and, growing there, set up inflammation and abscess, the process being similar to that which occurs in the formation of boils in adults, but being clinically distinguished from that by the tendency to form true abscesses, and by the absence of necrosis. Escherich believes that these differences depend on differences in the degree of tension of the skin in adults and infants, and more especially in atrophic infants, in which these abscesses are especially apt to occur. It is possible however that, as Baumgarten points out, the greater softness and irritability of the tissues of the child, as compared with those of the adult, play an important part.

The different course which is run by acute osteomyelitis, when it occurs spontaneously, and when it follows operations on bones, is also probably due, in the main, to the seat of inoculation. In the latter case we never see the scattered patches of necrosis which so frequently occur in the former, and this may be explained by the fact that, in the latter, the infective agents spread continuously in the tissue from the point of inoculation, whereas, in the former, they are carried by the blood, and may be deposited at various parts, thus giving rise to various foci of disease.

Another example of the influence of the seat of inoculation is the difference in the behaviour of the peritoneum as compared with the cellular tissue in regard to the pyogenic organisms. In former times the peritoneal cavity was looked on as one especially liable to inflame, and it was thought to be one of the chief triumphs of antiseptic surgery that operations could be performed on the peritoneum without bad result. The experience of a number of surgeons has, however, now shown that it is not absolutely necessary for success in operations on the peritoneum that all bacteria should be excluded from the cavity; in fact, this seems to be much less necessary than where operations are performed on other serous cavities, such as joints, or on the subcutaneous or muscular tissues.

The explanation of this surprising result is found in the nature of the lining wall of the cavity, and in the conditions under which pyogenic organisms find themselves there. The peritoneum has marvellous powers of absorbing fluids, and thus effusions into it are very rapidly removed, and in this way micro-organisms are deprived of the necessary nutrient material, while they are also, in all probability, absorbed along with the fluid and destroyed in the blood, or excreted. Wegner, who performed a number of experiments on this subject some years ago, has shown, in a very striking manner, the great absorptive power of the peritoneum.

I may mention one of his experiments. Two hundred cubic centimetres of warm serum were injected into the peritoneal cavity of a rabbit. An hour later the animal was bled to death, and the amount of fluid then present in the peritoneal cavity was only 66 cubic centimetres, no less than 134 cubic centimetres having been absorbed in one hour. Apparently the rapidity of absorption of fluid depends, in the first place, to a great extent, on the tension under which the fluid is, fluid under low tension, as when the walls of the abdomen are lax or when the fluid itself is small in amount, being absorbed comparatively slowly; and, in the second place, on the nature of the fluid, fluid of lower specific gravity than blood serum, leading, in the first instance, to transudation from the blood. If we contrast the condition of a wound in the cellular or muscular tissues in respect of its absorptive power, we find that we have not here an actively absorbing surface; in fact, the whole surface is for a few hours in the early stage of inflammation as the result of the injury done by the knife, and is not only not an absorbing surface, but is not even a healthy surface.

Wegner has also shown that a great variety of fluids free from bacteria, such as water, bile, urine, blood, etc., may be injected into the peritoneal cavity of rabbits without causing any bad results, and even large quantities of unfiltered air may be similarly introduced without setting up peritonitis, the air being soon absorbed, though by no means so rapidly as fluids. If putrescible fluids are injected into the peritoneal cavity at the same time that air is introduced, they rapidly undergo decomposition; but this is only the case if the quantity of fluid is too great to be quickly absorbed. Thus 15 cubic centimetres of putrescible fluid injected into the peritoneal cavity of a rabbit will usually be absorbed before decomposition has had time to occur; but if as much as 50 cubic centimetres are employed, then only a part is taken up during the first hour, and the rest furnishes a substratum for the growth of the organisms present in the injected air, and these organisms develop with extraordinary rapidity, and may cause the death of the animal from septic intoxication.

In none of Wegner's experiments with the injection of putrefying or putrescible fluids and air did peritonitis occur, and Grawitz, who has since investigated the matter, has directed special attention to the conditions under which peritonitis is produced. Apparently the explanation why Wegner did not obtain peritonitis, but only septic intoxication, is that pyogenic organisms are not frequently present in the air, and were, therefore, not injected along with it, and also that they only act under certain special conditions.

As the result of Grawitz's experiments, the following seem to be the facts of the case: in the first place, saprophytic bacteria are absorbed or destroyed by the peritoneum in relatively enormous numbers; where, however, the peritoneum is abnormal, or where the quantity of fluid is too great to be rapidly absorbed, and where the bacteria are able to set up putrefaction, the symptoms of septic intoxication, as described by Wegner, result, but these symptoms are unaccompanied by suppurative peritonitis. In the second place, pyogenic organisms, when injected in small numbers into the normal peritoneal cavity, and when suspended in such an amount of indifferent fluid as can be readily absorbed, cause no peritonitis. On the other hand, peritonitis occurs as the result of the injection of these organisms if the peritoneum is abnormal; or if, with a normal peritoneum, large numbers of pyogenic cocci are introduced, or if the cocci are suspended in too large an amount of fluid to be quickly absorbed. The necessary abnormal conditions of the peritoneum may be set up, at the same time that the pyogenic organisms are introduced, substances act which weaken or kill the tissue of the peritoneum, and thus provide a suitable soil for the penetration of the cocci; and above all, if there is a wound of the peritoneal wall in which the infective organisms can develop.

The factors, then, which are required to produce suppurative peritonitis are the presence of the pyogenic cocci—usually the streptococcus pyogenes—along with too large an amount of fluid to be rapidly absorbed, or along with disease of the peritoneum, or themselves in too large numbers, or acting in too great concentration. In other words, in order to develop peritonitis, the cocci must either be introduced in such numbers, along with their products, that a part of the peritoneum is at once injured, and thus ceases to exercise its normal functions, or they must be introduced into an unhealthy peritoneum, or they must be able to grow in the peritoneal cavity, either because fluid is present in too large a

quantity to be quickly absorbed, or because the absorptive power of the peritoneum has been diminished, or because some material, such as a piece of blood-clot or a piece of injured or dead tissue, is present, in which they can develop.

It is evident, therefore, that when authors draw conclusions to the effect that aseptic treatment is unnecessary in surgical practice, because they obtain good results in operations on the peritoneum when they take care to introduce as few of these organisms as possible (in many cases probably none at all are allowed to enter), to introduce them in as dilute a state as possible, to remove all the fluid and other materials, such as blood-clot, in which they can grow, and to avoid injury to the peritoneum as far as they can, they make an assumption which is not at all in accord with other clinical and experimental observations. The points which I have mentioned amply explain the results, and bring them into unison with those of experiments and of clinical experience with regard to other tissues of the body.

Indefinite Conditions on the part of the Body.—Further, we have conditions of a more indefinite character on the part of the body. Thus age, as we have seen, is an important factor in the production of acute osteo-mylitis. This is a disease of youth, and occurs most frequently between the ages of 7 and 20, and I have mentioned the different situations which are attacked in infants and in youths. Other diseases also vary in frequency at different ages; thus spontaneous erysipelas is apparently most frequent in persons between 35 and 45 years of age, and next most frequent between 45 and 55. Diphtheria most commonly occurs below 5 years of age, and steadily decreases in frequency as the age increases.

As regards sex also we find in some of these diseases a marked difference in the frequency of occurrence in the two sexes; thus spontaneous erysipelas is apparently much more frequent in women than in men. Eschbaum found, in 181 cases, that 122 of those attacked were females and only 59 were males. Osteo-mylitis, as we have seen, is most common in males.

It is possible that the state of the digestive organs may have an important influence on the occurrence of these suppurative diseases, as shown by Kocher's experiments and views on the production of acute osteo-mylitis. Kocher came to the conclusion, in the case of dogs, that after injury to bone this disease could be induced by feeding the animals with large quantities of putrid materials, and he thinks that in many cases of acute osteo-mylitis the starting-point is a disturbance of the digestive organs, permitting excessive multiplication of bacteria in the intestinal canal and their entrance into the blood. In fact, Kocher holds that an individual in whose intestinal canal fermentative changes of an intense character are going on is practically in the incubation stage of acute inflammation, which will develop if an injury or some other local depressing cause comes into play. In this way Kocher explains the occurrence of acute osteo-mylitis after typhoid fever, and he relates a case as bearing on this view, in which a girl, shortly after recovery from an attack of epidemic cholera, knelt for a long time in church, and was immediately attacked by acute osteo-mylitis of the tibia. Kraske, however, who has paid great attention to this matter in *post-mortem* examinations of cases of acute osteo-mylitis, and has carefully examined the wall of the intestine and the mesenteric glands, both microscopically and by cultivation, states that he has never been able to obtain any evidence that the infective material had entered the body by these channels. Whether Kocher's view is correct or not, the possibility that, during the progress of some wound or inflammatory disease, if the digestive organs are very much out of order, organisms may multiply to a great extent in the intestinal canal, and may enter the blood and thus reach the seat of the local disease or injury, is worth bearing in mind.

It is possible, also, that the nature of the diet may affect the occurrence of these diseases. It has been observed, for instance, in the case of symptomatic anthrax, that calves are more or less immune against this disease so long as they are fed on milk, but that, after this period has passed, and when their diet becomes exclusively vegetable, they lose their immunity. Arloing, Cornevin, and Thomas explain this by supposing that the milk diet induces a particular constitution of the body which is unfavourable to the development of this disease, but, on the other hand, this may be a mere coincidence, and the cause may be some peculiarity in the youthful connective tissue.

The state of the blood is also of importance; for example, the frequency of carbuncle and furuncle and of ulcerative and suppurative affections and their stubborn course in cases of diabetes

is well known. It is very probable that part of the explanation of this fact is the presence of the sugar or its chemical progenitors in the juices of the part, leading to the formation of a better pabulum for the development of the micro-organisms, though no doubt much depends on what we must more vaguely term the general depression of vitality of the tissues caused by the disease. Dilution of the blood also apparently interferes to some extent, though only slightly, with the rapidity with which bacteria are killed in it. Thus Von Fodor found that if, at the same time that non-pathogenic bacteria were injected, a quantity of water was introduced into the blood, the bacteria did not disappear so quickly as in undiluted blood. Pettenkofer, in fact, has come to the conclusion that everything which increases the amount of water in the body increases the predisposition of the individual to infective diseases. There is no doubt, also, that other chronic affections, such as albuminuria, predispose to septic diseases.

Acute diseases, such as acute fevers, also predispose to these affections, as in the case of the occurrence of acute osteo-mylitis after acute fevers, of pneumonia after typhoid fever, etc., probably in part because, as in the case of scarlet fever, the pyogenic cocci are able to enter and live in the blood.

Tension apparently has a considerable influence in causing inflammation and in predisposing to suppuration. The spread of an abscess after it has once completely formed is, no doubt, largely due to the tension of its contents; for the microscopical examination of the wall shows that the increase is not due to the spread of the micro-organisms, and, further, if an abscess is opened aseptically and well drained, the secretion of pus ceases. The same is seen in the case of wounds, where, if micro-organisms are present, the occurrence of tension from accumulation of discharge is apt to be followed by suppuration, and where, on relief of the tension, the suppuration ceases.

In some cases, however, the predisposition is apparently lessened as the result of the action of various indeterminate causes, and apparently, also, this lessening of the predisposition may be due to a previous attack of the same disease, though, as regards the organisms under consideration, erysipelas seems to be the only case where a temporary and partial protection is attained in this way.

We now come to the consideration of the conditions which more especially affect the bacteria, and which are not, perhaps, of less importance than those to which we have been alluding; these are chiefly the species, the dose and concentration of the organisms, the virulence, and the concurrent growth with other bacteria.

Influence of Species.—As regards the species, while, as we have said before, the nature of a disease does not, by any means altogether depend on the cause, it does so to a large extent; and all writers are now agreed as to differences in the pathogenic action of the pyogenic streptococci and staphylococci. These differences have been previously referred to, and it has been seen that the streptococci are generally associated with erysipelatoid processes, while the staphylococci tend to cause more circumscribed suppurations. The streptococcus is by far the most dangerous organism, and apparently has the property of creeping in the living tissue, spreading in it for a time without being noticed, and then setting up violent reaction. Fränkel has found streptococcus pyogenes in a great variety of puerperal diseases, especially in the so-called lymphangitic forms. It gains entrance to the cellular tissue of the pelvis from ulcers in the vagina, spreads in the pelvic cellular tissue, reaches the ligamenta lata and the peritoneum, and, spreading along the lymphatic channels, ultimately attacks the diaphragm and pleura; finally it reaches the blood, and causes septicæmia, pyæmia, suppuration in joints, etc.

As regards the other pyogenic cocci, I have already referred to the differences in their effects on animals, some of them not being pathogenic in rabbits, and some, such as micrococcus pyogenes tenuis, being especially associated in man with mild inflammations.

Dose and Concentration of the Organisms.—Perhaps the most important factor with regard to micro-organisms is the dose or numbers, and the concentration in which they enter the body. Ogston has already laid stress on the dose as explaining the different diseases which result from the introduction of these organisms, and he looks on the difference between acute abscess, and pyæmia as in the main a quantitative one. This, however, is only partially correct, as must now be evident.

Various authors have, from time to time, mentioned with regard to bacteria, that some act best, or only, when present in

large numbers, but the matter has not till recently been thoroughly worked out. I was led to investigate this matter in connection with some interesting experiments made by Sir Joseph Lister, which appeared to show that one or a few putrefactive bacteria could not set up putrefaction in blood taken with various antiseptic precautions, while that result was obtained if a mass of putrefying material was added to it. At first sight I did not think that it could matter much, except as regards the rapidity of the result, whether to begin with, one or a million bacteria were employed, but nevertheless I determined to put the matter to the proof, and to my surprise I found that difference in dose was a most important factor in the production and the type of many diseases. The experiments were made in such a manner that I was able to ascertain exactly the number of bacteria introduced, the material being in the first place diluted to such an extent that, on rough estimation with the microscope I obtained a general idea as to the number of bacteria present in a given quantity of the fluid; a certain amount of this fluid was then injected into the animals, and at the same time a measured quantity was thoroughly mixed with liquefied nutrient jelly which was then poured out on glass plates and allowed to solidify. By counting the number of colonies of bacteria which developed on these plates, each colony probably originating from a single bacterium, I ascertained exactly how many organisms were present in the amount of fluid injected.

Without going into further details, the following are the most important results that I obtained. In the case of Hauser's proteus vulgaris, I found that a definite and large dose of the cultivation in nutrient jelly was necessary to kill rabbits, and in comparing these doses, I took care that they were always injected into the same tissue, for example, the muscles, in accordance with the facts previously mentioned with regard to the importance of the seat of inoculation. I found that about $\frac{1}{10}$ cubic centimetre of an undiluted cultivation was a rapidly fatal dose when injected into the muscles, and I ascertained that this quantity contained about 225,000,000 of bacteria; $\frac{1}{10}$ cubic centimetre containing therefore about 56,000,000 bacteria, always caused an extensive abscess, of which the animals usually died in six to eight weeks. Doses of less than $\frac{1}{10}$ cubic centimetre produced no effect; in fact, doses of less than $\frac{1}{10}$ cubic centimetre, or, in other words, fewer than about 18,000,000 bacteria, seldom caused any result. From $\frac{1}{10}$ to $\frac{1}{2}$ cubic centimetre caused abscesses; above $\frac{1}{2}$ cubic centimetre caused death in twenty-four to thirty-six hours.—Further, the size of the abscess apparently depended on the initial dose. If $\frac{1}{10}$ cubic centimetre caused any effect at all, it was only a very slight trace of opacity which soon disappeared, while $\frac{1}{2}$ cubic centimetre caused a large and spreading abscess, ultimately resulting in the death of the animal, and intermediate doses produced abscesses intermediate in size.—Further, the concentration of the bacteric material is also of great importance, as shown by the fact that the dose must act at the same place, at the same time. It apparently will not do to split up the dose and inject various portions of it into different parts of the same animal at successive periods of time, or even at the same time. In both cases the effect of the smaller dose is produced.

I have tested this matter in the case of a number of other infective diseases, and have found that the result depended mainly on what we may, for want of better knowledge, term the predisposition of the animal to the disease. Thus in the case of mouse septicæmia, mice, which are extremely susceptible to this disease, die as the result of the injection of a single bacillus, while the only result of the injection of 4 cubic centimetres of a jelly cultivation, containing myriads of bacilli, into the base of the ear of rabbits, is to cause illness for a few days, along with slight swelling and redness of the part. In like manner, in the case of chicken cholera, rabbits die apparently as the result of the introduction of a single microbe, but a considerable number—some where between 150,000 and 300,000—are required to cause the death of a guinea-pig; and here again we meet with the fact that where the animal is less predisposed to the disease, we have different effects, according to differences in the dose. As I have said, 300,000 bacilli are apparently able to kill guinea-pigs; as the result of a smaller dose, down to 10,000 bacilli, suppuration follows their injection; below 10,000 bacilli apparently no effect is produced. In the case of staphylococcus pyogenes aureus, I have found that it was necessary to inject something like 1,000,000,000 cocci into the muscles of rabbits, in order to cause a rapidly fatal result, while 250,000,000 produced a small circumscribed abscess. The same result was obtained with staphylo-

coccus pyogenes albus, only apparently fewer cocci were required. In the case of the tetanus bacillus, death did not occur in rabbits when fewer than 1,000 bacilli were introduced.

I think that in these experiments a good deal depends on the simultaneous action of the products of the bacteria, and I would suggest the following explanation of the facts. When the animals are not very susceptible to the action of a bacterium, the cells and tissues soon gain the victory in the struggle for existence; but where a large number of bacteria are introduced at one place they grow for a time before they are attacked by the cells, and, growing there, each produces a small quantity of poisonous material. The products thus formed must interfere with the action of the cells, and thus enable the bacteria to gain a foothold. The more bacteria are introduced at one time the more of these products will be formed; the more extensive will be the foothold, and the more marked will be the result. Where only one or a few bacteria are introduced into a slightly susceptible animal, they are overpowered by the cells and quickly destroyed. When the number of bacteria is greater, these poisonous products destroy the tissues in their vicinity, and enable the bacteria to spread over a large area before the cells collecting around them are able to form an efficient barrier against their progress; and where the dose is very large no efficient barrier can be set up in time, and the death of the animal is the result. Thus the extent to which the organisms spread, and the violence of their action in animals not very susceptible to the disease, depend, first, on the number of bacteria and the quantity of products introduced in the first instance; and secondly, on the vitality of the animal and the rapidity with which a granulation wall is formed.

The facts made out in this research enabled me to lay down the following laws. In the first place, the pathogenic dose of a virus varies inversely with the predisposition of the animal to the disease in question; the greater the predisposition to the disease, the less is the quantity required, and conversely the less the predisposition the greater is the number of bacteria that must be introduced to produce the same effect. Of course the term "predisposition" is an absolutely indefinite one, but I have already discussed a number of conditions which go together to make up predisposition, and it is a convenient term, as expressing a complex set of conditions which undoubtedly exist, but about which we do not know very much.—A second law is that, in animals which are not very susceptible to a disease, the severity of the affection varies directly, within certain limits, with the amount of virus introduced. In all the affections of this class which I investigated, I found three stages, according to the dose injected: first, a stage where, with a small dose, no apparent effect was produced; secondly, an intermediate stage where a local affection resulted, the extent of the local affection depending to a great degree on the dose of the virus; and thirdly, a stage where, after a very large dose, death occurred. Of course, as predisposition varies in the same species of animal—for example, in man—we cannot measure out the dose nor calculate the effects of a given dose in each instance.

The importance of these facts as regards dose is very great in connection with our subject, for man is not very susceptible to the action of pyogenic organisms, and the results produced by them vary to a great degree in accordance with the second law. In the case of wounds, it is important to know that apparently in man a single pyogenic coccus might possibly do no harm, unless indeed it met with conditions, such as retention of fluid, under which it could grow. At the same time, I doubt if a single coccus ever enters a wound; as a rule they occur in masses containing many individuals, and then, of course, we have the effects of a large instead of a small dose. And there is no doubt that man is very much more susceptible to the action of these organisms than rabbits, and, therefore, a very much smaller dose will probably produce the same effect. These facts as regards dose probably explain to some extent the fairly good results obtained where, by imperfect attempts at antiseptic work, the introduction of gross particles of dirt, that is to say, of large numbers of bacteria, is avoided, and where, consequently, the effect of the injection of a small instead of a large dose of the virus is obtained.

The importance of dose has, as I have said before, been mentioned by various observers. Thus Ribbert, in his research on experimental myo- and endocarditis, already referred to, found that in order to obtain the desired result it was necessary to inject a considerable quantity of the cultivations. Thus a Pravaz syringe-ful of the emulsion killed the animals in from twenty to twenty-four hours; if the dose was somewhat less, the animals might live

even for five days; if only one-sixth of a syringe-ful was injected, the animals lived still longer, and endocarditis was not produced. —In the case of symptomatic anthrax, the relation of dose to the production of disease is extremely marked, a small dose either producing no effect at all, or only local reaction, which, however, may suffice to render the animal immune, while a larger dose causes the death of the animal.

Virulence.—It is also important to remember that organisms may vary in virulence at different times, and that the greater the virulence of the organisms the less are other conditions necessary to enable them to gain a foothold. A virus, or, at any rate, most viruses, is, as regards virulence, not a fixed quantity; it is, in fact, in a constant state of variation under the influence of the external conditions under which it finds itself. I need not refer to the well-known facts with regard to variations in virulence in the case of anthrax, chicken cholera, swine erysipelas, etc., as the result of the mode of cultivation employed outside the body; but I may mention some of the points which seem to bear especially on the pyogenic organisms. In many cases it is found that as the cultivations carried on outside the body become older, so the virulence of the organisms is apt to decrease. This is very well seen in the case of Fränkel's pneumonia coccus, which loses its virulence within two or three days, when grown in the same medium outside the body, and which, if its virulence is to be maintained, must be reinoculated frequently, and passed from time to time through the animal body. It can be readily seen, also, that staphylococcus pyogenes aureus grows most luxuriantly in the early cultivations from the body; but after it has been artificially cultivated for some time, its growth is by no means so rapid. Emmerich states with regard to cultivations of erysipelas cocci that they vary much in virulence, and that the longer the time between each fresh inoculation, the less is the virulence of the culture; in fact, the erysipelas cocci can be readily attenuated to such a degree that they can no longer kill mice.

It is important also to remember that where the virulence of an organism is diminished, its effects on animals vary in accordance with the second law; thus if a considerable number of attenuated anthrax bacilli are injected into rabbits the result will be, not a general fatal disease, but a local inflammatory affection, with possibly the production of abscess, varying in degree to a certain extent with the amount injected. In fact, the effect of the attenuated organisms on animals highly susceptible to the virulent virus is the same as if virulent organisms were injected into less susceptible animals, and consequently, in order to produce the same effect as the virulent organism, correspondingly large doses of the attenuated organisms are required. Thus Kitt and Hueppe have found that they could obtain the same result by injection of the organisms of an infective disease of deer into animals if, as the organisms lost their virulence, the number of microbes injected was increased. These facts are also important as showing how, even in a mild epidemic of a disease, where the virulence of the virus is not very great, bad cases may occur where extra large doses of the virus have been taken in, and this is probably in part the explanation of the occurrence of isolated severe cases in the course of a mild epidemic.

It is further important to remember that loss of virulence may not only be due to the ordinary conditions of growth, but may result from the action of various chemical substances. Thus carbolic acid and other antiseptics apparently diminish the virulence of anthrax bacilli, and it is possible that something of the same kind occurs with regard to the pyogenic cocci in wounds; and this may to some extent explain why, at the present day, although pyogenic cocci occasionally enter wounds treated aseptically, they sometimes do but little harm, less harm, in fact, than when they enter wounds in the treatment of which these antiseptics are not employed. It is quite possible that in growing in fluids containing a minute amount of an antiseptic, they are deprived, at any rate to some extent, of their virulence.

As regards increase of virulence, a very curious observation has been made in reference to the bacilli of symptomatic anthrax. It has been found that the addition of a minute quantity of lactic acid to a fluid containing these bacilli increases the virulence of a very attenuated virus within a very short time. Thus Arloing, Cornevin, and Thomas found that if to a fluid containing these bacilli $\frac{1}{1000}$ part of lactic acid is added, and the mixture allowed to stand for twenty-four hours, the pathogenic power is increased twofold; if then a little water, containing a very easily fermentable sugar, is added to the mixture, and another twenty-four hours allowed to elapse, the virulence has attained its maximum,

and frogs inoculated with this virus die in from twelve to fifteen hours, whereas when inoculated with ordinary virus they live forty to fifty hours. Kitt has repeated and confirmed these experiments, and he mentions the following: A small quantity of the vaccine material—that is to say, the attenuated virus of symptomatic anthrax—was divided into two parts, of which one was mixed with water, and injected into two guinea-pigs, while the other was mixed with the same quantity of water, to which three drops of lactic acid had been added; this mixture, after standing for six hours, was injected into the other two guinea-pigs. The result was that the first two guinea-pigs remained well, the virus being very attenuated, while the last two guinea-pigs died of typical symptomatic anthrax within twenty-four hours. With regard to this point, it is worthy of note that the pyogenic cocci, when grown in milk, for example, produced lactic acid, but, so far as I am aware, there is no evidence that, under these circumstances, their virulence is altered. Something of this kind may, however, be the explanation of Ogston's results; he found that if pyogenic cocci were grown in eggs, their virulence was increased, and he attributed this result to the absence of oxygen. I tested this matter with regard to the possible alteration in virulence when grown in various gases without being able to make out any noticeable difference; but it may be that, in Ogston's experiments, some chemical substance was present in the egg, or was produced by the organisms when growing in that material, which led to the increase in virulence. The fact with regard to lactic acid does not apply to the coccus of pneumonia, which, according to A. Fränkel, loses its virulence most quickly when grown in milk, and, in his opinion, this is due to the presence of lactic acid produced by them. Whether or not this fact has any bearing on our subject, it is worth remembering as showing what slight and unexpected causes may alter the virulence, and thus cause a difference in the result of the action of these organisms.

Concurrent Growth with other Bacteria.—We have also to consider the effect of the concurrent growth with other bacteria, and we shall find that the result may be either to increase or diminish the pathogenic action; in man, in all probability, the pathogenic action of the pyogenic organisms is generally increased. When two organisms grow together in the same medium outside the body, they either do not interfere with each other, or, what perhaps most frequently happens, one of them gains the upper hand in the struggle for existence, and, if a number of bacteria gain access to a wound, a struggle for the mastery at once commences between the different kinds. In wounds, this struggle in most cases probably ends in favour of the pyogenic cocci, and as the result of the concurrent growth other factors come into play which still further aid their action. Thus, although the pyogenic cocci gain the upper hand, the putrefactive bacteria may aid their action very much, for the products of putrefaction, when absorbed, act in an extremely poisonous manner, depress the vitality of the patient, and may thus enable the cocci to live in the body; and locally these products injure the young granulation tissue of the wound, and may thus open up an entrance for the pyogenic organisms. I have already referred to the experiments made by Grawitz and Scheuerlen on cadaverine and putrescine, products of putrefaction, and it will be remembered that the experiments showed that these substances, when present along with the pyogenic cocci, enabled the latter to obtain a foothold in the body.—The bad effects resulting from the concurrent growth of different kinds of bacteria is also very evident in tubercular cases. If a sinus leading to carious bone, the wall of which is lined with tubercles containing tubercle bacilli, becomes the seat of development of these pyogenic cocci, the result may be—in fact, generally is—a more rapid growth of the tubercle bacilli; and it seems that it is just in these septic cases, especially where irritating injections are also employed, that the danger of further and general tubercular infection is greatest, the local depression of vitality produced by the septic organisms enabling the tubercle bacilli to grow more luxuriantly.

Then also in some instances it appears that a mixed infection is more dangerous than a pure infection. Thus, in some cases the presence of more than one kind of pyogenic organism apparently increases the severity of the suppurative process. Kraske, for example, has observed in acute osteo-myelitis that the cases were most severe when the infection was a mixed one, that is to say, when the disease was caused not only by the staphylococcus pyogenes aureus, but where in addition "albus," and in some cases the streptococcus pyogenes, were also present; and, as a result of his observations, he thinks that the discovery of mixed infection

in acute osteo-myelitis ought to lead to a bad prognosis. Probably, also, one reason why we so seldom at the present day see the extremely bad septic cases formerly described is that, even where the treatment is not thoroughly aseptic, such precautions are taken as to exclude not only gross masses of dirt—in other words, large numbers of the organisms—but also a great mixture of them. And this is possibly also in part the reason why, in my first work on this subject, I was led to think that bacilli were of more importance in wounds than micrococci, for I observed that the wounds in which both organisms were present did not pursue so favourable a course as where the cocci alone were found.

Apparently, however, in some cases the presence of two species of pathogenic organisms is better for the animal than if only one species were present; and, although the facts as yet made out have no direct bearing on the production of suppuration, yet, as they are of great interest, and as something similar may occur in the case of the pyogenic cocci, I shall mention some of the experiments. A number of observers have attempted to utilise the antagonism which exists between certain species of bacteria in cultivations outside the body as a means of cure when the body is attacked by organisms, but till quite recently these attempts have not been followed by success. Emmerich, however, has lately performed some very remarkable experiments on rabbits, showing the value of the erysipelas cocci as a protective and curative agent against anthrax in these animals. For example, in one set of experiments rabbits were first inoculated with large numbers of the cocci of erysipelas, and then two to fourteen days later anthrax bacilli were introduced. Of fifteen animals treated in this way, seven recovered, while all the control animals inoculated with anthrax alone died; of the seven animals which died after inoculation of both organisms, some succumbed to the anthrax bacillus and some to the erysipelas organisms. The results were not so successful when, after anthrax had been set up and after symptoms of disease had appeared, erysipelas cocci were injected subcutaneously; but they were somewhat better where the erysipelas cocci were injected into the blood stream.—In a later paper Emmerich and Mattei communicated results obtained by injecting erysipelas cocci into the circulation and subcutaneously in rabbits about twenty-four hours before infection with anthrax. They found that in rabbits in whose bodies large numbers of erysipelas cocci were present, anthrax bacilli, though injected in enormous numbers, were destroyed in from twelve to seventeen hours, and could not be found either at the seat of injection or in the blood and internal organs, whether by microscopical examination or by cultivation. The bacilli were evidently unable to penetrate into the blood or internal organs, nor could they cause any local reaction or oedema; in fact they very quickly died out.—Perhaps still more remarkable are the experiments performed by Pawlowski. He found that, after injection of a mixture of erysipelas cocci and anthrax bacilli under the skin of seven rabbits, only two died. Pawlowski has also made the important discovery that the erysipelas coccus is not the only organism which interferes with the growth of anthrax in the body. Thus, ten rabbits were first inoculated with anthrax bacilli and then cultivations of micrococcus prodigiosus were injected subcutaneously into each animal on two occasions two and twenty-four hours after infection; of these ten animals, eight recovered. He also found that subcutaneous injection of anthrax bacilli and cultivations of the pneumonia cocci were not fatal to rabbits, and that subcutaneous injection of cultivations of anthrax bacilli and staphylococcus pyogenes aureus was not followed by the death of the animal; four rabbits treated with "aureus" recovered.

As to the explanation of these facts, Emmerich and Pawlowski come to very much the same conclusion. Apparently, with the exception of the pneumonia coccus, anthrax bacilli grow readily outside the body in cultivations containing also the other organisms mentioned, such as the erysipelas coccus. Hence the explanation cannot be that the erysipelas cocci *per se* prevented the growth of the anthrax bacilli in the body. It seems to be rather that these cocci irritate the cells of the body, the phagocytes, and increase their destructive power; it may be, as Emmerich suggests, that this irritation leads to a slight alteration in their physiological functions, so that they excrete some chemical substance which is very injurious to the anthrax bacilli.

How far these facts may be applied to the treatment of anthrax pustules in man, where either from the situation or the size of the pustule excision or cauterisation is impracticable, is a question very difficult to answer, but it seems to me that we must await

the results of further investigations before any attempt to apply them practically in man would be justifiable. In any case, the facts are well worthy of note as affording another example of what unexpected factors may come into play if we once admit organisms to wounds.

Local and Seasonal Conditions.—Lastly, we have certain local and seasonal conditions which appear, in some way or other, to influence the occurrence of some of these diseases. For example, Eschbaum, who has gone into this matter very carefully, finds that spontaneous erysipelas occurs most often apparently in February, then next most frequently in November, and least frequently in July. Apparently the cold months, and those where there is most moisture and greatest variations in temperature, show the largest number of cases, and Eschbaum summarises the facts by saying that the cases are most numerous when we have marked variations of temperature, with a medium height of the barometer and a high degree of moisture. In the case of diphtheria also, cold and moisture seem to be a great predisposing cause, most cases occurring about the months of November and December. Kocher and Lücke have found that acute osteo-myelitis also is most frequent in winter. Probably besides the seasonal conditions, the confinement in badly-ventilated rooms, foul air, and want of exercise which come into play more frequently in cold and wet weather than in summer, have an important influence on the result. In the case of diseases of animals, more especially in the case of anthrax, there is a very marked relation between the season and the outbreaks of the epidemic, the disease apparently occurring where there is great moisture and high temperature. As regards anthrax, Chauveau has shown that increased atmospheric pressure tends to cause a loss of virulence.

As an example of the influence of locality on these suppurative diseases, we have the greater frequency of acute osteo-myelitis in certain parts; for example, this disease seems to be more frequent in Berne than anywhere else, and, according to Volkmann, it occurs next most frequently in Halle, and then in Marburg; these, however, are rather impressions than actual statistical facts.

SUMMARY.

We thus come to the end of our considerations with regard to the factors involved in the production of suppuration and septic diseases. It must be admitted that our knowledge still shows many blanks, but nevertheless, enough has been gained to enable us to judge what are the most essential factors which come into play. That the pyogenic organisms are essential for the production of these diseases as they occur naturally there can no longer be any doubt; but in many cases much depends on other conditions, of which the chief probably are the dose or number of the organisms and their concentration, general and local depression of vitality, and the seat of inoculation. If the organisms enter in large numbers, sufficient to overcome the resistance of the body, they alone may cause the disease; frequently, however, they enter in smaller numbers, and then other conditions become necessary to enable them to act. Of these conditions the chief are, as I have said, depressed vitality—either local or general—combined with the possibility of their remaining in the weakened tissue. This depression of vitality may be brought about by conditions acting on the body generally, such as acute fevers; or by local conditions, more especially those which induce the early stage of inflammation, such as cold, injury, chemical substances, the products of the bacteria themselves, or the products of other kinds of bacteria which may happen to be growing along with them. Or again, the favourable condition may be some peculiarity in the soil, as shown by variations in the character of the disease in accordance with the seat of inoculation and the anatomical arrangement of the part. The only factor, however, as I have said before, with which we can reckon with certainty, is the cocci themselves.—I need not enter into details as to the pathology of all the various suppurative and septic diseases, it will be easy for anyone to apply the facts which have been stated to each case; but in conclusion, I should like to make one or two remarks with regard to the mode of entrance of these organisms into wounds.

OCCURRENCE OUTSIDE THE BODY.

These organisms are fairly widely distributed outside the body. In the air they have only been found on a very few occasions, and in very small numbers. Staphylococcus pyogenes aureus has been found on one or two occasions in the air of surgical wards, as has also the streptococcus of erysipelas. Experiments have been made as to the presence of the latter organism in the air of

wards in which erysipelas patients were present, and they have in one or two instances been found in small numbers; as a rule, however, they are apparently present only when the patients are in a state of convalescence and when desquamation of the skin is occurring, and it seems highly probable, from the observations that have been made, that they are carried in the cutaneous scales thrown off during desquamation. Erysipelas cocci have also been found in a *post-mortem* room where cases of erysipelous infection had occurred, and in this case the infection was supposed to have come from the floor. The pyogenic organisms are very rarely present in putrefying fluids, but they have been found on decomposing beef, and in the water employed in kitchens for rinsing dishes; they are also sometimes present in the superficial layers of the soil. One of their most common seats outside the body is the surface of the skin, and they especially occur in parts where the skin is moist, for example, in the axillæ, between the nates, between the toes, etc.; they are also frequently present in connection with the hair, and in the dirt beneath the nails. Fränkel has found them in the secretions of the healthy pharynx, and Bockhardt found "aureus" and "albus" in large numbers in the nasal mucus of a patient suffering from chronic catarrh of the nose, and, at the same time, affected with syphilis of the upper lip.

MODE OF ENTRANCE INTO WOUNDS.

As regards the entrance of these organisms into wounds, they may get in during an operation from the air, from the instruments and hands of the operator or his assistants, from surrounding objects, or from the skin in the neighbourhood of the wound. We are now, however, sufficiently acquainted with the various precautions necessary to prevent the entrance of these organisms, and it is a comparatively easy matter to leave a wound made through a previously unbroken skin without any pyogenic organisms in it.

In the after-treatment of wounds there are two situations where the battle with these parasites may take place; it may either occur outside the wound, the organisms never being allowed to enter it, or it may take place inside the wound after their entrance has been permitted. It is hardly necessary to remark that in case of war we try, if possible, to carry the war into the enemy's country, at all events, we do all we can, by guarding the passes and borders, to prevent the enemy from entering our own country; and in like manner, in the case of wounds, it seems to me that it is much better to keep these pyogenic organisms out of the wound and to do battle with them outside the body, than to let them enter and trust to the efficacy of the tissues to repel their attacks. For once they have entered the wound, it is but little that we can do to aid the action of the body, and what little we do do has to be done with extreme caution, for not uncommonly our efforts, instead of being of service, do a great deal of harm. As I have said, it is comparatively easy now to keep these pyogenic organisms out of a wound while it is being made, and to leave the wound without any of these microbes in it; the problem is to prevent their entrance afterwards. In this case, however, we have at any rate succeeded in transferring the field of battle from the interior of the wound to the surface of the body, and we have no longer to trust to the imperfect and but little understood action of the tissues; we can step in with vigorous action without any fear of doing harm. For it cannot be too much insisted on that antiseptic dressings are not, in their essence, applications to wounds; they are applications to the discharge which has come from the wound and to the skin around it.

As to the mode of entrance of these pyogenic organisms after the operation, they may get in while the dressing is being changed, either by falling in from the air, though this must be of rare occurrence seeing that they are so rarely present in the air, or by contamination by the surgeon's hands, instruments, etc.; but this is also very easily avoided, and ought not to occur. Usually they spread in either through the dressing or beneath it during the interval between the change of dressings. In my opinion they most commonly spread in by growing in the discharge which is lying between the dressing and the skin, and in the superficial layers of the epidermis, more especially in the latter; for as the result of the irritation of the antiseptic employed there is hypertrophy of the epithelium, and thus a large number of dead epithelial cells are present, which, being soaked with the discharge, form a good nidus for the development of the bacteria, unless, indeed, enough of the antiseptic has been communicated to the discharge and the epithelium from the dressing to render it an unsuitable soil for the growth of organisms. If this is not the case, the organisms

will go on growing in the substance of this dead epithelium, protected by the superficial layers from the action of the dressing, and thus they may, if a dressing is left on for too long a time, ultimately reach the wound. This is not a mere theoretical speculation, for I have been able to trace the development of the organisms beneath the dressings, from their margin towards the wound, the extent to which they spread varying with the length of time that the dressing has been applied.

If these views as to the mode of entrance of bacteria into wounds are correct, it follows that it is very important when a dressing is changed to wash and thoroughly disinfect the skin around the wound as far as the dressing extended, and beyond it, with an antiseptic lotion, care being of course taken by covering up the wound not to infect it while so doing. If this is done, then at each change of dressing the field of battle is transferred from the neighbourhood of the wound to the margin of the dressing, and in accordance with the size of the dressing, this battlefield will be at a greater or less distance from the wound.

I shall not enter any further into the subject of the treatment of wounds. We have now at our command a large number of antiseptics which more or less answer the purposes required, and it is only by careful attention to the exclusion of these organisms that we can obtain the best results. That we can completely exclude these bacteria from wounds—both at the operation and afterwards—I have been able to ascertain by numerous experiments; and that, just in proportion as we are successful in so doing, we are to a like degree freed from the occurrence of suppuration and septic diseases, and can to a like degree reckon with confidence on rapid and painless healing of wounds with the least disturbance to the patient, is a matter now of everyday observation.

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CASE OF CEREBRAL ABSCESS IN CONNECTION WITH OTITIS MEDIA, SUCCESSFULLY DIAGNOSED AND EVACUATED.¹

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THE case which I have the honour to bring before you this evening is one of the few cases of cerebral abscess in connection with disease of the middle ear which have been accurately diagnosed during life, and successfully treated by operation. For though abscess of the brain is a very common occurrence in connection with inflammation of the ear, and perhaps more frequently in chronic affections of this kind, it is generally the subject of *post-mortem* record, rarely accurately localised during life, and still more rarely treated successfully.

I have only been able to find two cases of a similar nature. One of these has been recorded by Gowers and Barker (*JOURNAL*, December 11th, 1886). This was a case of abscess in the right temporo-sphenoidal lobe, diagnosed without external indication, beyond the fact of inflammation of the ear, and successfully evacuated. The second has been recorded by Greenfield (*JOURNAL*, February 12th, 1887). This was a case of abscess situated in the anterior part of the left temporo-sphenoidal lobe, in which, in addition to the general indications of abscess, there were symptoms of pressure on the third nerve, a fact which prohibited the localisation of the seat of the abscess.

Two others have been referred to by Greenfield, namely, a case reported by Schondorff (*Monatsschrift für Ohrenheilkunde*, 1885, No. 2); and a second by Truckenbrod (translated in *Archives of Otolaryngology*, June to September, 1886). In both these cases, however, there were, in addition to the general symptoms, external indications of the seat of the abscess in the form of localised pain and oedema of the skull, and a fistula leading from the primary seat of disease.

The fistula in Truckenbrod's case led only under the pericranium to a rough place on the outside of the bone, while in Schondorff's case it led directly into the brain, and indicated the way by which the pus had penetrated. These two cases therefore are to be placed in a different category from those of Gowers and Barker and Greenfield; but a successful result was obtained in all.

Of the successful result in the case I bring before you this evening you will all be able to convince yourselves, as the quondam patient is here, and apparently as well as he has ever been.

On the evening of December 8th, 1887, I was asked by Mr. T. W. Coffin to see with him a case under his care, the history of which he related to me, and subsequently gave me the following detailed notes.

T. H., aged 47, a skilled artisan, was first seen by Mr. Coffin on November 25th. He had been ill since November 10th. On the 15th a discharge, somewhat offensive, had come from the left ear, which continued for about eight or ten days. When first seen he

was in a drowsy condition, but was capable of being roused, and replying to questions put to him. He complained of pain over the left side of the head, forehead, and back of the eyes, with a considerable degree of photophobia. The pain on the left side of the head was interrupted by pressure and percussion. There was slight discharge from the left ear, but the ear could not be thoroughly examined on account of the tenderness. The pupils acted normally, and vision appeared unaffected. There was no motor or sensory paralysis. The pulse was 52, weak and intermittent; respirations 14, laboured and sighing. The temperature was normal.

Mr. Coffin ordered the ear to be syringed with weak Condy's fluid, and prescribed a stimulant.

Next day the patient was brighter. He had less pain in the head. He was able to sit up in bed and smoke a cigarette, but he continued very drowsy and slept much.

On the 27th, 28th, and 29th he was still improving. The temperature was normal, the pulse regular, and the tongue cleaner, under the influence of a saline mixture and small doses of mercury. The discharge from the ear was more copious than it had been. There was very little tenderness on percussion of the left side of the head. The patient was generally asleep, but would rouse up for an hour or so, and occasionally smoke a cigarette.

On the 30th he was more drowsy, and apparently unwilling to be disturbed. At times it was very difficult to rouse him at all. He complained of more pain at the back of the eyes and general headache. His pulse was 60, respirations 16, and temperature absolutely normal.

On December 1st and 2nd the condition was essentially the same. There was no increase in the headache, but the drowsiness was greater.

Early on the 3rd he had become temporarily delirious, and had fallen back exhausted, but during the rest of this day and next there was no noteworthy change in the symptoms.

On the 5th, Mr. Coffin thought there was slight weakness in the right angle of the mouth, but so slight that it was considered somewhat doubtful by those who were acquainted with the usual expression of face.

On the 6th, for the first time there were indications of affection of speech. He used wrong words, and seemed angry at not being understood when he asked for what he wanted.

It was on the evening of the 8th that I saw the patient. He was at that time less drowsy and much clearer in his intellect than he had been for some time previously. He was able to sit up in bed, and talk, but his words were incoherent and for the most part unintelligible. He appeared to understand simple questions, but at other times appeared confused and unable to understand. He called things by wrong names. When asked to read a few sentences from a journal placed before him, the words he uttered had little or no resemblance to those before him.

There was no appreciable defect in the mobility or sensibility of his limbs, but the right angle of the mouth acted less energetically than the left. Examination of the eyes, carried out with some difficulty, revealed signs of optic neuritis, but a more thorough investigation of this and other conditions was reserved till the following day. From the facts, however, related to me by Mr. Coffin, and the patient's condition as seen by myself, I confirmed the opinion passed by Mr. Coffin that it was a case of abscess of the brain, in connection with disease of the middle ear, and I considered that the position of the abscess was fairly indicated by the symptoms.

The case seemed to me to be one which ought to be dealt with speedily, and I advised immediate removal to the hospital, with a view to further careful investigation and operative measures. The patient was removed the next morning to the National Hospital for the Paralysed and Epileptic, under my care. At this time he was conscious, and complained of no pain anywhere. He replied to questions, but frequently used wrong words without seeming to be aware of the fact. He occasionally hesitated to do what he was told, appearing as if he had some difficulty in understanding what was said to him. There was perceptible weakness of the right angle of the mouth, and though he could make every movement with his right hand, it was found that the grasp of the right hand was only 80 lbs., whereas that of the left was 100 lbs., the patient being a right-handed man. The tendon reactions were active on both sides, and there was no appreciable difference between those of the left and right. There was no affection of sensation. Ocular movements were normal, and the pupils equal and contractile. Ophthalmological examination

¹ Read before the Medical Society of London, March 5th, 1888.