A LECTURE

ON THE

ARTIFICIAL PRODUCTION OF TUBERCLE
IN THE LOWER ANIMALS.*Delivered at the Royal College of Physicians, May 15th.*

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THE next organ which presents marked changes is the liver. It is greatly increased in size, and feels heavier than natural. In it are seen two or three sets of changes, which, however, I think, all belong to one type. The chief of these is the appearance of a tissue of a glistening semitransparent character, which occupies the substance of the organ to a variable extent. Sometimes it only occurs in little specks, of the size of a pin's head or a poppy-seed; sometimes it is in larger masses; sometimes it runs in lines, mapping out the acini very distinctly; sometimes it is found in regular masses in which there is no trace of liver-structure visible to the naked eye; or the conditions before described may be reversed, and lines of natural looking liver-tissue may be seen running irregularly through the semitransparent tissue.

In the first of these cases, the disease might almost suggest the idea of cirrhosis; in the second, that of an albuminoid liver; but it differs from the cirrhotic liver in being crisp and friable and destitute of all toughness, and from both it and the albuminoid liver in the fracture being finely granular. Moreover, the tissue never stains with iodine; and in all these places the new growth has an appearance which more or less shews that it was originally composed of fine granulations. In other cases, the granulations are not confluent, but are scattered thickly through the liver-tissue. They do not project from the surface, and the peritoneum is not, as a rule, thickened.

In some places, where the former class of changes predominate, there are seen irregularly in the liver-tissue spots of a dead opaque white, sometimes surrounded by a zone of injection. Their section is finely granular, not smooth like those next to be described, and they appear to result from a fatty degeneration of the acini.

There are also seen, both in the larger tracts of semi-transparent tissue and also when this change only occurs in the form of granulations, spots of cheesy change. These may be either seen occupying only the area of individual granulations, or they may extend through considerable areas. They generally, however, remain firm and hard. In some cases—though the appearance is rare—they may form masses of the size of a hazel-nut, with a diffuent creamy centre.

When sections of the liver are examined with the microscope, the semi-transparent portions, whether in granules or in confluent masses, are found to consist of a new growth situated in the interlobular tissue, or in what is called the capsule of Glisson between the acini. The tissue thus produced consists of cells uniformly imbedded in a delicate fibrous network, in the meshes of which they lie. In size, they correspond to the cells found in the new growths in other situations; the ordinary size being from 1-3000th to 1-3500 of an inch in diameter. Some may reach the size of the 1-2000th to 1-2500 of an inch. The nuclei average about the 1-3600th of an inch. They are very refractory, and have a distinct margin. The contents of the cells are nebulous, and their outline is less distinct than that of the nuclei. In some of the larger cells, double nuclei may occasionally be seen. In some places, the cells are agglomerated into strings or rows, forming elongated masses resembling those described as seen in the granulations occurring under the skin, and to which the same interpretation is probably applicable.

The amount of this tissue between the acini varies. Sometimes these are occluded over large spaces, or outlines only of the acini pressed aside may remain mapping out the masses of new formation. The sections under the microscope show that these latter always tend to assume a globular form, and that at their margins the cells of new growth, which are strikingly different from the liver-cells, pass up in lines between the network of cells of which the acini of the liver are composed. The liver-cells appear to atrophy in consequence of the progress of this growth, but they undergo no further changes. There is no multiplication of their nuclei, as if they participated in the new growth. There is no special granular change. They become pale and nebulous, with a fine mole-

cular appearance; and here and there some fatty change when they are pressed upon by the growth. Both the bile-ducts and the proper gland-tissue appear to be otherwise unaffected and healthy. Little specks of fine granular degeneration may be seen scattered through the masses of new growth, which in some spots pass into a more complete molecular debris.

The spleen also enlarges very much; sometimes to two, three, or four times its natural size. I have measured it two inches and a quarter long, one and a quarter broad, and half an inch thick. It also is greatly increased in weight. This organ also presents various appearances. A very common one is, that small whitish spots are scattered thickly through the whole tissue. These appear of about twice the size of the normal Malpighian bodies. Another consists of agglomerations of these normal bodies into masses, which have then a racemose appearance.

Other masses are seen more opaque, but having the same structure of agglomerated granules. The spots of smaller size have generally a certain transparency, but less than is observed in the liver or in the lung. Sometimes large tracts of the spleen are converted into a semi-transparent brittle tissue resembling that of the liver or of the lymphatic glands, and shewing also an appearance as if originally composed of fine granulations.

Various forms of cheesy change are also found. These in some places occupy about the same area as the smaller granules, and are seen as scattered, yellow, dry, firm spots, brittle, and crumbling under pressure into a granular mass. The larger compound granulations may similarly become cheesy and opaque. Cheesy spots, of variable size, may also be seen scattered through the semi-transparent tissue. In rarer cases, large irregular tracts may become cheesy, still maintaining the same firm, dry, friable, and opaque character. In yet rarer instances, large portions of the spleen are found changed, like those of the liver, into masses of the size of a hazel-nut (which is the largest I have seen), and composed of a diffuent softened amorphous material; but, in such cases, semi-transparent granulations and cheesy granulations are seen in other parts of the organ.

The large cheesy masses are not very distinctly separated from the surrounding tissue, and are not surrounded by any zone of injection. They differ also considerably in the character of the softened material and in the absence of abruptness in their limitation from anything known as pyæmic spots. Under the microscope, most of the granulations seem to be composed of enlarged Malpighian bodies undergoing various stages of fatty degeneration. The whole tissue is also infiltrated with cells precisely resembling the lymphatic cells of the spleen. Together with this increase of cells, there may be found, in the more transparent areas, fibrous changes analogous to those described in the lymphatic glands.

The changes in the intestines mostly affect the small intestines and the cæcum. In the former, the patches of Peyer are enlarged, and they are prominent externally. The peritoneal surface is injected, and sometimes thickened, and through it numerous opaque white spots can be seen. Internally, also, the patches are enlarged and prominent, and the mucous membrane around is injected and opaque. Milky-white spots are seen scattered in the substance of the patches. Ulceration also occurs in specks in them, but it seldom affects the whole patch.

In the cæcum, the patches are also much enlarged; but the single follicles are less distinct than in the small intestine. Ulceration of the whole or of portions of the patch are not uncommon; and, when present, they have often a cheesy floor, in which are numerous small granulations, like those seen in the floor of a tuberculous intestinal ulcer in man. Thickening of the margin is less marked; but, with this exception, they present all the characters of the tuberculous as contrasted with the typhoid ulcer of the intestine. In explanation of this, it may be stated that the mucous membrane of this portion of the intestine is much thinner in the guinea-pig than in man. The solitary glands of the small intestine are occasionally enlarged; sometimes also they are cheesy.

Microscopic examination of Peyer's patches in the stage of enlargement shews cells crowded in the follicles in a manner similar to that observed in the lymphatic glands and in the spleen, and in many parts undergoing fatty degeneration. Once I have seen a bloody slough adhering to the ulcerated surface, and once punctiform extravasations in other parts of the mucous membrane of the intestines. With the last exception, I have seen no other signs of hæmorrhage. The ulcers always spring from Peyer's patches or from the solitary glands, and not from other parts of the intestine. The stomach has always been unaffected.

The mesenteric glands are almost invariably affected, even when distinct changes are not discoverable in the intestine itself. One gland shows this most prominently; viz., the large one situated in the part of the mesentery attached to the ileo-cæcal valve. The large glands in the hilus of the liver and the gastro-hepatic omentum are also very commonly affected. Their changes are similar to those of the axillary glands.

In the peritoneal cavity, dropsy is very common. Lebert attributes it to the obstruction of the circulation through the liver, and I think with reason. I have once seen hæmorrhage into the cavity. I could not discover its source; but all the branches of the portal vein were loaded with blood. The chief change, however, to which I wish to direct your attention in this part occurs in the omentum. Here, scattered thickly through the tissue, are found granules varying in size from a pin's point to a poppy-seed, seldom much larger. They precisely resemble the grey granulations found in tuberculous peritonitis in man, except that I have only once found any sign of inflammatory action attending the process. This was in a case of general tuberculous peritonitis following abortion.

Under the microscope, the granulations are found scattered in the course of the vessels, and they then originate in the perivascular sheath. They are also, however, to be found in parts of the tissue where no vessels whatever are to be seen, and here they appear to have their starting point from masses of nuclei or cells agglomerated among the meshes of the omentum, which appear normally to occur in scattered points of this tissue. From both sources, the growth extends irregularly to the surrounding tissue; and, whatever their origin, whether from the sheaths of the vessels, or, independently of these, the only further change discoverable consists in a dense agglomeration, most commonly of the nuclei, and sometimes of the cells, in the meshes of the network of which the omentum is composed. With this exception, I have never been able to trace any distinctive characters which separate the histological characters of tubercle in the omentum from that of the healthy surrounding tissues. I have never seen anything like an epithelium covering the omentum, as distinct from any nucleated tissue beneath. The only appearance which we can see in the normal omentum is that of cells (the outline of which is often indistinct, and of which the nuclei alone may be visible) imbedded in the meshes of a fibrillated tissue—a structure which strongly resembles that which ordinarily is called "lymphatic tissue". The cells, both in the normal and also in the tubercular omentum, vary somewhat in size; but their average is between 1-2400th and 1-3200 of an inch in diameter.

Let me present you briefly with a summary of the number of times in which these appearances have been found. Out of the 117 cases, three internal organs have been affected fifty-eight times; in six, less than three. Out of these sixty-four cases, local granulations at the site of injury have been stated to be present forty-one times. They were absent in all the doubtful cases. They were absent in the case of general tubercle following the insertion of a cotton-thread, though the fibrous tissue in which this was imbedded presented some indistinct traces of their appearance. They were absent, also, in three out of four cases, where tubercle followed the insertion of a cotton-thread saturated with vaccine-lymph. They were never present when no certain internal effect was produced, except in one doubtful case in a rabbit.

The local lymphatic glands are noted to have been affected with induration and cheesy spots in fifty-four cases. In one or two of the doubtful cases, there was induration; in two others, enlargement, but no other change. In three others of the doubtful cases, they were distinctly affected. They are only stated to have been absent in four cases of general tuberculous; and I should almost question the accuracy of my own observations, whether I may not have overlooked one or two enlarged glands in these instances.

The lungs have been affected in fifty-nine out of the sixty-four. In one, they were unchanged, when the spleen alone was affected; in one, when the liver, spleen, intestines, and mesentery were affected; in one, when the liver and spleen suffered; in another case, the affection was doubtful in its nature.

The bronchial glands escaped only eight times out of the sixty-four; twice only when there was any amount of lung-affection present.

The spleen has been affected fifty-nine times, only escaping five times out of the whole group.

The liver has been affected fifty-one times. In nine, the character of the affection was considered doubtful, consisting only of cheesy spots, which in some cases appeared to be due to sporesperm, and where no other distinct affection could be discovered. In four, it was altogether absent.

Of the omentum my notes are less perfect. It was affected twenty-five times. The condition was not stated in twelve cases.

The intestines were affected in twelve cases; not examined in twenty-two. In the rest, though examined, no affection was found.

The mesenteric glands were affected forty-five times out of the sixty-four.

These results may be contrasted with twelve cases of inoculation in rabbits. I inoculated five with pus without producing any general affection; but in nearly all these there was extensive local suppuration under the skin. Inoculations with tubercle, seven in number, only produced distinct

effects in two; and these were mixed with pneumonia and with other internal inflammations. I mention these to show that the affection in the guinea-pig is much more easily produced than in the rabbit.

I must now pass somewhat briefly over a point which deserves to be dwelt upon at greater length than my time will allow. It refers to the correspondence of these growths with what is ordinarily considered not as tubercle; and, in discussing this, I will take as the type of tubercle that pathological product concerning the nature of which there is the least difference of opinion—viz., the grey granulation. There are, however, two or three leading points which I should wish to lay before you with some emphasis. One of these includes the mode of distribution, the multiplicity of the affection, the organs affected, and the individual parts of the organs so affected, which strikingly correspond to the chosen seats of tuberculous affection in man. There is one exception in the guinea-pig—viz., the absence of meningeal affection; but I do not think that this can weigh very materially against the cumulative force of the argument derived from the other viscera. And I think that the non-implication of the meningeal arteries in the guinea-pig may depend on minute points in their anatomy with which we are not yet familiar.

I would also point out to you that, in all these organs, the main character of the affection is that of a growth resembling the lymphatic tissues, and probably having its starting-point in structures of this nature. Now I think that, if there is one definition of tubercle which we can hold by more strongly than another, it is that of Virchow, who has pointed out the analogy between tubercle and lymphatic structures; viz., that it consists of round cells, of many of which the nuclei alone may be visible, imbedded in a network either of fibres or of a more transparent but semi-cartilaginous-looking homogeneous tissue; in which, however, distinct fibrillation may be absent.

Another point is, that these growths are agglomerated into little masses, like the follicles of lymphatic glands, or the Malpighian bodies of the spleen, or the solitary glands of the intestines; that, wherever they occur, they tend to form distinct granules, but that at their margins they blend insensibly with the surrounding tissue; that they extend in connective tissue by a change in the mode of growth of this tissue, through which cells are produced resembling rather those of a lymphatic gland than of the connective tissue itself; that they have no specific character, in this resembling those of tubercle; that they pass into an early decay, which is not sloughing, but molecular death; and that this degenerative change appears to be caused partly by their mutual pressure and by the density of the growth, and partly by the occlusion of vessels. I think that we know of no other growth except tubercle, of which all these attributes can be predicated, and certainly none other which occludes the vessels of the part to the extent which is effected by these formations in the guinea-pig.

My time is too short to permit me to discuss with any minuteness the question of the identity of the morphological structures of these growths in the lung with those of human tubercle. One fact may, however, I think, be very distinctly stated—that we are not dealing with any "lobular pneumonia", any "catarrhal pneumonia", or with any infiltration of the interior of the alveoli (which are the very last parts that are occluded). The growth proceeds by a progressive thickening of the walls of the alveoli, which finally closes the air-vesicles. Even in the densest masses, when examined with a binocular, a certain transparency can be distinctly seen, in some places showing that central portions of the alveoli are still hollow. There is very little participation of the epithelium in the growth. The epithelium seems, if I may say so, to disappear in the progress of tubercle, and to give place to cells of another and different character. I think (if I may digress for a moment) that we have been dealing with the question of the epithelium of the lung in too specific a sense; and that, in the alveoli, it is only a derivative of the connective tissue, like the cells which I have described in the normal omentum, and having but little resemblance to the appearances of an epithelium in a mucous membrane which rests on a nucleated subjacent tissue. In the alveoli of the lung, no subjacent nucleated tissue can be seen; but the cells lining them appear to be the sole representatives of cell-forms (with the exception of the nuclei of the capillaries and of some fusiform nuclei), in the delicate membrane of which the wall of the alveoli is composed. Under certain morbid processes, especially of the catarrhal type, they enlarge and desquamate; and we then call them epithelial cells which have separated. At other times, however, the structure no longer produces epithelial cells, but cells which are the direct derivatives of connective tissue. A few large cells like epithelium are occasionally produced; but these latter do not, as a rule, form a large proportion of the grey granulation in the lung. The epithelium passes away, or, at any rate, does not maintain its type in the process of the new growth. There is no filling of the alveoli—at least, not to any proportionate extent—with epithelial forms; and thus far we have not been dealing with anything like ordi-

nary pneumonia, and the process is absolutely dissimilar from that of pyæmia.

It appears also that, in the lung, the point of departure of the growth is in no essential respect from the vascular apparatus; nor is this implicated in the same manner as it is in most inflammatory processes. The point of departure, even when it is connected with the vessels, is in a tissue external to the vessel; and the occlusion of the circulation which occurs round the growth is either through pressure, or by the implication of the walls of the capillaries in the growth; and it passes backwards from them to the smaller arteries, and not in the converse direction.

I think that there can be very little question but that the affection in the lymphatic glands is one so closely akin to the tubercular change, that I need not dwell upon it further.

The organ which might excite most doubt is the liver, because, in man, tubercular growths in this organ very seldom proceed to the same extent as is observed in the guinea-pig. But really, in its essential characters, this growth appears to me to be identical with that of tubercle in the human liver. Their seat is the same; their relation to the acini is the same; and in both we see the same immunity of the proper liver-structures from all participation in the process of the new growth; and I think I may say that we know of no other disease except tubercle to which the description I have given of the growth in the liver can apply. The only one producing at all analogous effects in the liver is leucocythæmia, and to that I will allude in a few moments.

As regards again the omentum, any one who will compare for a moment one of these growths with specimens from the human omentum, or from that of the monkey, can have, I think, but very little doubt remaining as to their perfect histological identity. They are in both cases perivascular, and also extravascular, and they both equally pass gradually into cheesy decay.

In conclusion, I think I may say that any one who doubts whether these growths are tubercular is bound to show that a hitherto unknown disease affecting the rodentia, excited by special agencies, occurring in all the organs in the chosen seats of tubercle in man, occurring with equal frequency in them and in the same parts of these organs as in man, growing with the same general features of histological character, and having the same vital characters and the same early degenerative cheesy change—not suppurative nor ordinary acute softening,—and yet that this disease is not tubercular. The only disease which possesses the least affinity with it is leucocythæmia; but leucocythæmic growths have the same tendency to degenerative changes, and they are, as an almost invariable rule, attended with an increase of the white corpuscles of the blood, which these growths are not. Tubercle also is similarly unattended, though it might be expected that it would be, from the implication of the lymphatic apparatus.

I do not think that the disease can be considered as by any means identical with farcy, though the local changes may bear some resemblance to farcy changes; but every subsequent change of farcy is one of a suppurative kind in internal organs.

After the recent specimens which I have submitted to you, I do not think that any one can maintain that these changes can be included under anything ordinarily understood by the term pyæmia.

The great difficulty in the present day in identifying any disease with tubercle depends, I think, on defective, and, as it seems to me, somewhat arbitrary definitions of tubercle. I think, if I may pass such a criticism without presumption, that some modern pathologists are rather disposed too strictly to limit the application of the term tubercle. I think even that Virchow's careful observation, to which we owe so much—that all cheesy matter is not tubercular—has been pushed in the present day to an almost dangerous extreme; and that some pathologists are even disposed to doubt the tubercular character of any cheesy matter; whereas, on the contrary, tubercle is among the most frequent, though by no means the sole cause of such products in the body. Indeed, in some respects, these limitations of tubercle have proceeded so far that, if the exclusion of the different forms from the category of tubercles proposed by various pathologists were simultaneously carried out, tubercle would, not, unfortunately, cease to exist, but would certainly no longer have any place in our nosologies; for nearly every pathological product hitherto ranked under this title, from the grey granulation to the yellow granulation and the cheesy infiltration, is by some authority or other excluded from the category of tubercle. I would not for a moment say that I think no limitations to the class of tubercle desirable; but I think that we are at present in danger of carrying these to an extreme degree. At present, I think that in some respects—though I hope I shall not be accused of undervaluing the use of histological investigation—our naked-eye criteria are almost, if not quite, as valuable as the minute histological distinctions which have of late been set up. My impression is, that tubercle is a product which undergoes transformation in various directions; but that, though it varies somewhat in appearance, especi-

ally in the lung, according to the rapidity of its growth, or the greater or less amount of implication of epithelial structures in the process of its growth, and though it may, at one stage of its growth or transformation, present appearances different from those observed at another, yet that these stages and varieties of appearance are not the less tubercle.

There is, however, another point to which I desire especially to call your attention, in relation to the question of the identity of the disease in the guinea-pig and in man. This question appears to me to rest on a broader basis of analogy than that of the correspondence in every line and shade of description between the statements of individual observers, as regards either the histological characters of these growths in the rodentia and those of tubercle in man. Looking at the general history of histological research, I cannot for a moment flatter myself that I have exhausted all the points in the minute anatomy of these new formations; though I think that I have, so to speak, been able to lay before you the leading features of their ultimate structure. But what I wish to insist on is the general or constitutional character of the affection, which coupled with the general analogy of the new growths with tubercle, I think, almost absolutely proves their tubercular nature. It is not a question of the lung *alone*, or of the liver *alone*, or of the lymphatic glands, or the spleen, or the omentum or intestines considered singly. It is a question of a *general* disease, producing in all these organs growths which, if they occurred in man, would by ordinary observation be considered tubercular, and as no other disease is known except tubercle producing these effects. And therefore I think that, considering the identity of these with all the most important features of tubercle, we cannot but admit the tubercular character of the disease thus artificially produced.

[To be concluded.]

ACUPRESSURE IN CANADA.

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In the latter end of May of 1867, I took leave for a few months of hospital and private practice, partly to rest, and partly to note the changes that had taken place in practical medicine and surgery during the fourteen years that had elapsed between my present intended visit and a former somewhat lengthened residence in Great Britain, France, and Germany. The facilities of travel enabled me to spend a week or two here and there with some of my former preceptors, or with those who had taken their places in the intervening years. Men may write, and men may read; but I have always found a short interchange of thought with the living voice more valuable than long intercourse with those written auxiliaries—books. The changes in thought and action appeared to my mind to have been both numerous and important; and in another place, and at another time, I shall briefly notice what appeared to me most noteworthy; how, in Germany, Langenbeck had inaugurated a new era in operative surgery; how, in France, surgeons (*grâce à Dieu*) had become less diligent in their interference; how, in Italy, the severe depletive measures had in many places given way to a more enlightened practice; how, in Great Britain—that great crucible for reducing other nations' theories to practice—men had learnt to trust more to, and to aid, Nature in ridding the system of maladies she could not tolerate; how, in fine, medicine had become simplified, and surgery less meddlesome.

And now, casting my eye over what appeared to me most valuable and important, the method of arresting hæmorrhage from cut arteries, first made known to the profession nearly eight years ago by Sir James Simpson, stands out in bold relief. I had read, in medical periodicals, Sir James Simpson's descriptions, and those of Drs. Pirrie and Keith; but, teeming as the columns of medical journals are now-a-days with novelties which soon pass away and are forgotten, I had not practised, nor had I seen practised by others, a method which, in simplicity and safety, far surpasses any hitherto devised for arresting hæmorrhage. A spouting artery is closed with a pin or a needle that causes no inconvenience, gives no additional pain, is unattended with heat or swelling, is not followed by suppurative or any of the troublesome complications which sometimes occur to vex and alarm the ablest surgeons. During my ten days' residence in Edinburgh, much of my time with Sir James Simpson (whose kindness shall ever remain fresh in my memory), I saw what I had never seen before either in my own practice or in that of others—large wounds, requiring closure of the orifices of several bleeding vessels, uniting kindly and entirely by first intention throughout their whole extent. A lady had her breast twice removed, the first time for scirrhus, and the second time for a return of the disease. The first