A LECTURE

ON THE

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

By WILSON FOX, M.D., F.R.C.P.,

Holme Professor of Clinical Medicine at University College, London.

I WOULD now desire briefly to call your attention to the mode of the production of these growths. It is not my intention to propose any distinctly new theory; for the subject has received so many theories already that it would require a considerable exercise of mental ingenuity to found a new one. Still, however, there are, I think, certain legitimate conclusions which may be drawn from these experiments, if it be admitted that these growths are tubercle.

In the first place, M. Villemin's position that tubercle is a specific disease producible by tubercle alone cannot, I think, be held to be true; nor can the method of inoculation be used as a test of the tubercular character of any pathological product; for the four guinea-pigs in whom the vaccine lymph was inoculated, and those inoculated with putrid muscle, and even one beneath whose skin I simply inserted a piece of cotton-thread, and also one of the four in which, following Dr. Sanderson's example, I inserted a seton, presented as intense and typical specimens of the disease as those on whom inoculation had been practised with the most typical grey granulations from the lungs or the meningeal vessels.

Secondly, the results of all experiments hitherto conducted, as far as they have yet been carried, appear to show that, for the production of the disease, septic matters in a certain state, introduced into or produced within the economy, are necessary. I say septic matters; for I am inclined to believe that the effect of the seton, or even of the cotton-thread introduced under the skin, is produced by these substances setting up an inflammatory action, the products of which have the same influence as the other unhealthy substances which the list contains. The failure in many cases of these inert matters to produce such effects would appear to my mind strongly to bear out this view, which is especially corroborated by the cases where setons were inserted. In three of these, the setons ulcerated out and the skin healed, and all these cases proved failures, shewing that the infecting property probably depends on a certain kind of inflammatory action produced.

I may here perhaps be allowed to advert to the series of M. Lebert's experiments with matters directly introduced into the circulation. He injected mercury and charcoal into the vessels, and also quotes two experiments of older date in which, after repeated injection of pus into the veins, he found what he considered tubercles in the lungs and liver. M. Lebert argues that the effect of all these experiments was to produce tubercle; but, I think, some striking differences exist between the results of these experiments and the effects of inoculation, and the difference I notice is this, that there is no evidence to be found of a constitutional affection having been produced in any of these cases whose details he has given at length. It is on the *constitutional* affection and the *multiple* implication of many organs, that I lay especial stress in reasoning on the proof of the tubercular affection produced by inoculation. Multiple affections did not exist in any of M. Lebert's experiments, with the exception that, in the two dogs into whose veins pus was injected, some granulations, like tubercle, were found in the lungs and liver; but the authenticity of the tuberculous nature of these was not decisively established by microscopic proof. Perhaps, also, I may add that, in the innumerable experiments of this nature that have been conducted with a view to the illustration of the nature of pyæmia, the production of tubercles—*i.e.*, of grey granulations—has never been noticed, or, if at all, they have not been observed with a frequency sufficient to establish the possibility of this method of their origin.

The experiments with charcoal and mercury appear to me to be equally inconclusive. Out of ten experiments of this nature, in four only was there a production of local granulations in the lungs, which originated in thickening around the obstructed vessel, but sometimes extended beyond this; in one only of these there were found a few granulations in adhesions of the pleura, which did not contain mercury. In none, however, was there any implication of other organs; and, in this re-

spect, these cases present so marked a difference from the effects of inoculation, that I cannot but believe that in them tuberculosis was not produced as a constitutional disease. Local thickening around an obstructed vessel is not necessarily tubercle; and the same criticism is, I think, applicable to the introduction of mercury or of other irritating substances into the bronchi. The effect has been a local inflammation; but not either local tubercle or a general constitutional affection. Another important difference to be noticed in these granulations is the fact recorded by M. Lebert, that the vessels around them were not obstructed in the manner observed in tubercle.

As to the manner in which septic substances act, there is room for a wide diversity of opinion. One effect seems to be established, if the tubercular character of the granulations under the skin be admitted; viz., that a special local irritant is capable of producing local tubercle; and the suspicion naturally arises, whether this be not the starting point of the whole process. If, however, the character of these granulations be doubted, still the affection of the lymphatic glands in the neighbourhood has so strong a resemblance to that which occurs in these structures when secondary to tubercle in other parts, that it would appear either to confirm the tuberculous character of the granulations, or to carry the point of origin of the tubercular infection only one stage further forward.

One fact also deserves to be brought especially into prominence; viz., that the effects of infection are more certainly produced by the inoculation of tubercle than by that of other substances. The whole series of primary inoculations of this nature succeeded when the animals lived long enough to allow of the affection of their internal organs; and the series of twelve re-inoculations of tubercle artificially produced had the same results. It does not, however, appear that the mode in which tubercle of the latter class had originated produced any difference in the certainty of the effect of the re-inoculation. Tubercle produced by the inoculation of putrid muscle reproduced tubercle with the same certainty as that originating from the inoculation of the grey granulations.

Whether any direct effect can, in virtue of this superior infecting property, be ascribed to tubercle, must remain, I think, an open question; but it does not appear impossible that it may have in some way the power, when thus introduced, of directly propagating itself, similar to that observed in actual practice, when there is great probability that the multiplicity of the affection may be due to secondary infection of distant organs from that primarily implicated. And the points to be noticed with regard to tubercle—though this possibly may not prove very material—is that it is capable of thus producing infection when inoculated in a perfectly fresh state from an animal just killed. It should also, however, be noticed that the low forms of pneumonia, which were formerly classed with the tubercular products in the lung, appear to possess this infecting property in an equally high degree.

Whether the infection of the system is by chemical or mechanical means, whether it is produced by fluids or solids, by cell-forms, "germinal matter", or amorphous material, must remain, I think, a matter of hypothesis, in which the minds of individual observers will incline to one view or the other, according to the bent of their special pathological theories, but which has not, as yet, received any absolutely satisfactory elucidation. An experiment of Dr. Waldenburg's, in relation to this question, is, however, deserving of mention. He has found that colouring matters introduced under the skin together with the infecting material, are reproduced in the growths of new formation; but even this scarcely appears to afford an absolute proof that the infection is communicated by solid particles, though the presumption would appear to be in favour of this hypothesis, since the absorption of colouring matter by new growths is only what is observed under many different circumstances in the animal economy.

I may, perhaps, be permitted to say, as will perhaps appear from the remarks that I have already made, that the morbid processes I have now been describing appear to me to be absolutely removed from the ordinary phenomena observed in the obstruction of vessels by emboli. I have already stated that the obstruction of the vessels is a consequence and not a cause of the growth, and the anatomical appearances observed differ widely from embolic phenomena. When a vessel is obstructed from within, there results a centre of anæmia and of early necrobiosis surrounded by a zone of injection; while here there is an area of growth, generally proceeding from certain limited centres, but surrounded by a zone not of hyperæmia but of irregularly extending anæmia.

In speaking, also, of septic absorption as a mode of production of tubercle, I think that we must admit that these changes are to be placed in a different category from the phenomena ordinarily classed under the term of pyæmia. There is not a sign of suppuration to be observed in these cases—at least, not in internal organs; and so infrequent are the appearances of ordinary inflammation observed, that they may be

* Concluded from page 527 of last number.

almost said not to exist—at any rate, as an essential part of the process. M. Lebert speaks of the changes in the lung as a peri-bronchitis, or a peri-alveolitis, or a peri-arteritis; but all new growth is not inflammation. The inflammatory nature of tubercle, affirmed by Broussais and Cruveilhier, has been a ground of contention among pathologists since the writings of the former appeared; but, at any rate, we may affirm that, if the nature of the growth be inflammatory, it is an inflammation proceeding under special conditions and with peculiar limitations to individual tissues and to special parts of individual organs.

I must confess that the theory advanced by some recent pathologists since Dr. Cohnheim's researches on the exit of the white corpuscles from the blood-vessels, that the growth of tubercle is a result of this process—a theory, be it remembered, originally to some extent advanced by Dr. Addison of Brighton—does not appear to me to be supported by observations on these growths. The complete obstruction of the vessels in their neighbourhood would militate against this view of their origin; and a considerable amount of evidence may be found in some parts of the growth that their increase is due to the enlargement and subdivision of pre-existing cell-forms.

To sum up the conclusions which the facts appear to warrant regarding the origin of this process, I would say that the growths produced appear to originate from an abnormal nutritive activity of tissues either demonstrably lymphatic in their nature, or of those whose lymphatic character is a matter of probable inference; that this increased growth is caused by septic matter introduced into the system, and especially affecting these tissues by an irritative action; that the new growths thus produced conform in many particulars to the lymphatic type, but, growing under abnormal conditions or with perverted activity, they speedily pass into degenerative decay. This action, however, once excited, tends to repeat itself in the economy, either by virtue of the results of this degeneration possessing properties similar to that of the material whose morbid influence first excited the diseased process, or through direct infecting properties of the new growth transmitted either by the blood to distant organs, or, as in the case of the lymphatic glands, by means of infection through the lymphatic vessels.

This theory of the effects of septic matter is not altogether new. It was originally propounded by Dittrich as an explanation of the cause of tuberculation, and again by Buhl; the former of whom believed that the septic infection producing tuberculation was due to the retrograde metamorphosis of any morbid pathological products; the latter attributing it only to retrograde changes in tubercle once produced. (Virchow, *Krank. Gesch.*, ii, 722-3.) It finds, however, for the first time, its direct proof in these experiments. They also illustrate what clinical experience has recently led Professor Niemeyer to assert, that tubercle of the lung may be a secondary consequence of unabsorbed pneumonias. They illustrate, also, what has been the result of frequent surgical experience; but was first, as far as I am aware, distinctly stated by Mr. Holmes, at the Children's Hospital, that the removal of diseased bone prevents the formation of tubercle in predisposed subjects. (*Lancet*, 1865, i, 60.)

There appears, however, to be another element necessary in these cases, and that is a constitutional state predisposing to these effects. This is well illustrated in the different susceptibility of the guinea-pig and the rabbit; the former being much more prone to be thus affected by these agencies than the latter. In fact, I think it probable that it is to this cause that the failure of M. Villemin's experiments with other materials than tubercle, and which were conducted upon rabbits, is to be attributed.

I think, however, it requires to be stated, that neither guinea-pigs nor rabbits are naturally by any means specially prone to tubercle. Zoologists and comparative anatomists, of whom I have asked the question, have not noticed this disease among them. They have long been the subject of physiological experiment, but tubercle has not been noticed among their common diseases. M. Villemin's experiments also showed that only the inoculated rabbits thus suffered. I have kept large numbers of guinea-pigs during the last six months, and many rabbits; but not one has died tuberculous, except those inoculated. As a further test, I killed six non-inoculated guinea-pigs, taken without selection; and not one presented a trace of the changes found in the inoculated animals. The failure also of nearly half of the experiments with inoculation, most of which animals were killed, and in which no trace of tubercle was found—viz., fifty-three animals out of one hundred and seventeen—proves strongly that tubercle is not naturally a common disease among them.

In what the predisposition may consist, must remain to some extent an open question. I admit that I am strongly inclined to regard it as depending on some peculiar anatomical or physiological condition of the lymphatic system, which renders it specially prone to react under septic agencies. Both the lung and also the omentum of the guinea-pig are largely endowed with lymphatic structures—more so, I think,

than are to be found in these organs in man; but positive proof of this kind is very difficult of attainment.

The fact of special aptitude for the action of poisons in particular individuals, remains, however, a very positive one. It is shown by the escape of some of the inoculated animals when the same material was used more than once; and the effect of this in some special cases of other poisons which affect the lymphatic tissues, is well illustrated in the case of typhoid fever—a disease which especially attacks the young, while those past middle life have a greater comparative immunity. The explanation of this has long been taught at University College, by Sir William Jenner, to depend on the progressively diminishing nutritive activity of the follicular apparatus of the intestines and spleen with advancing life, rendering these structures less liable to be influenced by this specific poison.

The relative susceptibility of different genera of animals to this class of agencies has not yet been the subject of any extended experiments. Those hitherto made have been principally conducted with tuberculous matters, but without any very positive results. In one case only is general tuberculosis in a dog recorded by M. Rostan as a result of this proceeding. In other cases, as in a lamb and a ram by M. Colin, tubercles were found only in the lungs; and the same result was twice observed by M. Villemin in cats. M. Lebert also once observed granulations in the lungs of a dog which was the subject of a biliary fistula, and in which he injected phosphoretted oil into the rectum. But local growths in the lungs alone, though possibly tuberculous in their nature, do not, as I have before stated, afford the conclusive proof which I think that we at present require, and which is yielded by the multiplicity of the affection in many organs. In other animals, as in a goat, a cock, and a wood-pigeon (Villemin), or in a crow, cat, and fowl (Vogel), the experiments hitherto conducted have been without results. It would appear desirable that these should be conducted on a yet more extended basis.

In conclusion, I would venture to observe that I think we should not be too hasty in drawing conclusions that the method of production of tubercle now partially elucidated is the sole cause of the production of the disease. I cannot, for my own part, but feel that only a very small tract of a wide field of inquiry has been as yet opened for research; but I feel also that it is one that will repay the energies of the most careful and attentive observers; and that, as the mode and origin of this disease is more fully explored, we may, I think, indulge in the not unphilosophic hope that, with the discovery of its causes, we may find means at least for its prevention, if not in all cases for its cure.

Description of Figures illustrating Dr. Fox's Lecture on the Artificial Production of Tubercle.

FIG. 1.—From a subcutaneous granulation (page 501). Commencing at the lower left hand corner and extending obliquely upwards to the

Fig. 1.

right, is a dense mass of nuclei and cells agglomerated into an irregular row, and banded by a limiting "membrane" (?). Externally in the fibrous tissue towards the right hand are imbedded fusiform cells, tending to

become round, and with round nuclei. In many places the nuclei alone are visible. At the extreme left are large cells with double nuclei. Multiplied 1000 diameters.

Fig. 2.

FIG. 2.—From same. Cells like those last described seen free, multiplied 1000 diameters.

FIG. 3.—The larger figure represents growth of tubercle from the wall of a bronchus (p. 501). The section is carried transversely through the bronchus at its bifurcation. The wall of the bronchus at the lower

Fig. 3.

part of the figure is marked by cartilage-cells; external to this is a mass of round nuclei and round and fusiform cells mixed. Further from the bronchus, these are seen thickening the walls of the alveoli; multiplied 600 diameters. The figure on the right is a portion of the same where the vessels are not yet obliterated; multiplied 1000 diameters. Lines of fusiform cells are seen running along the capillaries. The epithelium can be seen in parts, as on the left side near the upper part, to be still unaffected.

FIG. 4.—Growth of tubercle around an artery of the lung (p. 501). Transverse section. The tubercle is here seen to consist of densely agglomerated nucleated cells, varying somewhat in size. Fusiform cells are also seen among them. Fusiform and round nucleated cells are seen extending among the meshes of the capillaries, and in some places obliterating them. At the left, is a capillary obliterated, with enlarged nuclei in its wall. Multiplied 1000 diameters.

FIG. 5.—The upper figure represents (p. 525) a section of the liver; it shews acini pushed aside by the new growth in the capsule of Glisson. At the right hand, about midway, is a part where the growth has probably proceeded from a deeper part than the plane of the section, and shews the manner in which it passes between the liver-cells; which is also seen at the left hand near the lower angle. In many parts, the rows of cells forming the acini are pressed aside by the growth; but, in others, the growth passes between the liver-cells. Near the centre are bile-

Fig. 4]

Fig.

ducts, with their columnar epithelium unchanged, multiplied 100 diameters. The lower figure represents a part of the new growth shewing a mass of cells and nuclei of elongated form, constituting a cord-like body, like those seen under the skin, multiplied 1000 diameters; and a part of the new growth multiplied 1000 diameters, shewing cells imbedded in a trabecular work of fibres.

FIG. 6.—A small nodule from the omentum of the guinea-pig, seated at the bifurcation of a small artery. In the denser part around the artery little is to be seen but a closely packed mass of nuclei. The nuclei lie imbedded in the broad bands of fibrillated tissue, of which the

Fig. 6

omentum is composed. Even in the denser parts a reticular arrangement of the growth is thus preserved, but the open spaces are diminished in size. At a greater distance, the growth is still seen to originate from the same nuclei, which lie in rows imbedded in the fibres. In some places, an outer cell-wall around the nuclei is visible, the cells being large and round. Multiplied 1000 diameters.

ERRATUM. In last number of JOURNAL, May 30, p. 526, second column, sixth line, instead of "what is ordinarily considered not tubercle," read "what is ordinarily considered to be tubercle."

ALCOHOL IN THE TREATMENT OF PNEUMONIA.—M. Pécholier, in a work lately published by him on this subject, expresses his opinion as follows: "We hold it to be demonstrated, by facts and arguments, that the beneficial action of alcohol in certain kinds of inflammation, and specially in certain kinds of pneumonia, is, in the first instance, due to the stimulating action of this agent. We, therefore, accept a portion of Todd's theories, without falling into his exclusiveness. If, in all cases of pneumonia, the vital powers are not always greatly weakened, as the English physician asserts, there exists a kind of pneumonia in which the radical forces are destroyed, and in which curative reaction requires to be stimulated. For this kind of pneumonia, Dr. Todd's prescription is proper; in others, it is useless, and sometimes even injurious."

CONTRIBUTIONS TO THE HISTORY OF MEDICINE.

By AQUILLA SMITH, M.D.,

Professor of Materia Medica and Pharmacy in Trinity College, Dublin.

I.—ON THE TREATMENT OF CORYZA, OR NASAL CATARRH, BY "A TOTAL ABSTINENCE FROM LIQUID."

DR. CHARLES J. B. WILLIAMS, in the article "Coryza" published in the *Cyclopaedia of Practical Medicine* in 1833, after giving the usual treatment by aperients, diaphoretics, and diluents, adds: "It is the acrimony of this discharge (from the pituitary membrane) which reacts on the membrane and keeps up the inflammation and its accompanying disagreeable symptoms. On this circumstance depends the efficacy of a measure directly opposed to that just noticed, but to the success of which we can bear decided testimony—we mean a total abstinence from liquids." "This method of cure operates by diminishing the mass of fluid in the body to such a degree that it will no longer supply the diseased secretion." "The coryza begins to be dried up about twelve hours after leaving off liquids; from that time the flowing to the eyes and fullness in the head become less and less troublesome; the secretion becomes gelatinous, and between the thirtieth and thirty-sixth hour ceases altogether. The whole period of abstinence needs scarcely ever to exceed forty-eight hours."

Assuming that priority of publication of opinions or experiments is justly entitled to the merit of originality, and without any intention of detracting from Dr. Williams's acknowledged reputation, I proceed to show that, in his method of treating coryza, he was anticipated by an eminent English physician at the close of the seventeenth century.

The author, in *Tractatus de Corde, cui accessit Dissertatio de Origine Catarrhi, in qua ostenditur illum non provenire à Cerebro, autori Richardo Lower, M.D., editio tertia et ultima, Amstelodami 1671*, in cap. vi, De Catarrhis, says: "Cum vero catarrhi materia, occasio atque organorum in eo secernendo ministeria ex præmissis constiterint; satis obvium et facile erit concipere quod illi sistendo aptissimè conferet..... In quantum igitur ex sero sanguinis materia catarrho suppediat, quicquid ei pabulum detrahit, aut serum per renes præcipiat, vel per alvum derivat, vel per poros corporis dispellit, intentioni curativæ apprime satisfacit. Quare quum catarrhus primo urget, nihil majus ei supprimendo conducit, modo absque febre sit, quam ut sitim diutissimè toleremus; tridui enim vel quadridui abstinentia à potu plures novi à catarrho prorsus liberatos, cujus alia ratio non est, quam quod fomite subducto omnino exsiccatur, non aliter ac rivuli exarescunt ex pluviarum penuriâ." (P. 234.)

In the extracts from Dr. Williams's article on Coryza, the words in italics are his own; and in the quotation from Lower I have put a few words in italics to shew the parallelism.

ON IODIDE OF METHYLE AND THERAPEUTICAL RESEARCHES.

By JAMES TURNBULL, M.D., Liverpool.

I OBSERVE in the BRITISH MEDICAL JOURNAL of April 18th, a report of a meeting of the Medical Society of London, at which Dr. B. W. Richardson presided and exhibited a specimen of iodide of methyle, which, he thought, promised to prove of the greatest use in practical medicine. He also made the statement that the iodide was first experimented with physiologically by himself last year, and was reported on by him to the meeting of the British Association at Dundee. It is proper that I should correct this statement and the error into which Dr. Richardson has unwittingly fallen; * for if there be any merit in being the first to investigate the physiological properties of this and other allied compounds, I ought to assert my claim to it, having read a paper, at the meeting of the British Association for the Advancement of Science held at Liverpool in 1854, entitled "Researches on the Physiological and Medicinal Properties of some of the compounds of the Organic Radicals—Methyle, Ethyle, and Amyle." The paper was afterwards published in the Association MEDICAL JOURNAL, where, in the volume for 1865, page 69, the following account of the properties of iodide of methyle is given.

"Iodide of Methyle.—The next compound of methyle, the iodide, is a

* April 22nd, 1868. Since this was written and sent to the Editor of the JOURNAL, Dr. Richardson has in the most handsome manner rectified this mistake by a statement made at the subsequent meeting of the Medical Society of London.—J. T.