CONDENSED REPORT OF A

Lecture

ON

TUBERCULOSIS AND TABES MESENTERICA.

Delivered before the Hon. the Grocers' Company in the University of London, July 9th, 1888,

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THE lecturer began: "Sir James Paget and Gentlemen,—When the Hon. the Grocers' Company did me the honour of electing me to one of their scholarships, I set out with a light heart and bright anticipations to continue some researches on the subject of Tuberculosis in general, and Pulmonary Phthisis in particular, which I had initiated some little time before. Under the influence of my teachers in the Edinburgh school, and under the inspiration of the researches of Koch (which had so recently been published), Burdon-Sanderson, Wilson Fox, Baumgarten, Klein, and others, whose works I was reading, I aspired to go into the whole subject of tuberculosis. Since that time my ideas, I need hardly say, have assumed less ambitious proportions, the area of my investigations has been considerably limited, and I have been content to take one or two points for consideration in the first instance, leaving the remainder for further investigation as time and opportunity offer. In the present lectures I shall attempt to give an outline account of part of the work on which I have been engaged during the last two years. I say part of the work, for I intend to leave the experimental work, except where absolutely necessary for purposes of elucidation, for further consideration. The subjects of tuberculosis and phthisis have, from earliest times, received the attention of our best observers, and in this country, where the conditions are specially common, much has been written, and many most valuable treatises have come from the pens of these observers. With all this, however, the intimate connexion between certain conditions was never made clear until we had Koch's detailed experiments on tubercle as a point from which to start further observations."

He then went on to point out that the presence of tubercle nodules, though latent, in any part of the body, now comes to have a much greater significance than formerly, as each mass of tubercle, whether recent or caseous, must be looked upon as a focus from which invasion of any part of the body may take place. It was with this in view that he was led to make a most careful examination of all the material that fell into his hands, to see what light could be obtained on the subject.

Writing recently on the subject of phthisis, Dr. James pointed out that the "general mortality is excessive at birth, rapidly diminishes till about the fifth year, more gradually till about the fifteenth, and then first slowly and then rapidly rises to the end; the phthisis mortality shows during the early years of life a comparatively low rate, a rapid rise from fifteen to twenty-five, and then a somewhat gradual decline." During the first five years of life he believes that errors of diagnosis are specially common, but all the errors tend to an under-statement rather than to an over-estimation of the number of deaths from tuberculosis of some form or other.

As an outcome of the whole of the more recent observations, tuberculosis has come to be looked upon as the result of a specific morbid irritant, acting on tissues which are so far devitalised that they are not able to cope with this irritant. Although Metschnikoff's views on this subject have been referred to, especially in connexion with the more acute specific infective diseases, it never seems to have been fairly grasped except by those who have made a careful and special study of tuberculosis, that what holds good in the case of micro-organisms in the more acute specific diseases may be equally true as regards the action and reaction of the bacillus tuberculosis and the tissues in the human body; that the battle of the cells and bacilli may go on as really and as continuously in

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the case of tubercle as it does in a localised anthrax or in a suppurating wound; and that the conditions for the development of the tubercle bacillus in the human or animal body must be just as definite and as favourable to the existence of that bacillus as they must be to the development of the organisms of pyæmia or allied processes. Of these conditions the lecturer mentioned the following—(a) Some weak point in the epithelial surface at which the organisms, now generally admitted to be the cause of tuberculosis, may invade the deeper tissues in sufficient numbers to be able to hold their own in the struggle for supremacy that ensues. (b) The comparatively low vitality of these deeper tissues, the cells of which they are composed being no longer able to deal successfully with any large number of bacilli that can under ordinary circumstances find their way so far. It should be borne in mind that, although tubercle bacilli are so widely disseminated, they are under ordinary conditions seldom present in sufficient numbers in the atmosphere to render them in any way formidable to any but the most unhealthy (as regards tissue resistance) individuals. It was pointed out that it is a matter of common observation that tubercle affects different organs at very different periods of life; or, at any rate, that in tuberculosis certain organs are more frequently affected, and at an earlier period of the disease, than are the rest. For example, tubercular meningitis occurs much more frequently between the third and the eighth years than it does at any other period of life. Rilliet and Barthez give the results of the examination of 98 cases of this condition. They state that during the first year there were only 2 cases; between one and two years and a half, 17; from three to five years and a half, 34; from six to seven years and a half, 23; from eight to ten years, 15; and from eleven to fifteen years, 7 cases.

Of 54 cases of tubercular meningitis examined by the lecturer, not one was under one year (adopting the same classification); between one and two years and a half there were 15; from three to five years and a half, 21; from six to seven years and a half, 8; from eight to ten years, 8; and from eleven to fifteen years, 2. These figures corresponded fairly closely, and might serve as a basis for comparison. In these 54 cases, tuberculosis was in 39 so widely disseminated that it might fairly be said to be general; in only 2 cases could no primary centre of infection be found. In 6 the only foci that could be primary were to be found in the lymphatic glands of the mediastinum alone or along with those of the mesentery; in 3 the lungs were the only other organs affected; and in 1 the lungs and mediastinal glands contained the older tubercle nodules.

In the brain or in its membranes, the embolic tuberculosis must be looked upon as part of a general process. Intestinal tubercle, it was stated, is said to be most common in the years following childhood from twelve upwards for six or seven years. From an analysis of 127 cases of tuberculosis in children it was found that in 43 instances there was tubercular ulceration of the intestine. During the first year after birth there was only 1; between one and two years and a half, 14; from three to five years and a half, 10; from six to seven years and a half, 7; from eight to ten years, 5; and from eleven to fifteen years there were 6. So that in this series of cases the intestines are frequently affected during very early life as well as in somewhat later years. Although the intestines are directly affected by tubercle in such a small proportion of cases, the mesenteric glands are found to be in some stage or other of tubercular degeneration in no less than 100 instances, or in nearly 79 per cent. of the whole. This was considered to be a point of sufficient importance to be worthy of special note. The age at which these tubercular glands in the mesentery were found is also significant. During the first year of life there were 4 cases; from one to two years and a half, 33; from three to five years and a half, 29; from six to seven years and a half, 12; from eight to ten years, 13; and from eleven to fifteen years, 9 cases. Here, again, the figures are higher during the earlier periods than during later years, but the maximum is reached (as with ulceration of the intestine) at a distinctly earlier period than in the case of tubercular meningitis. In 14 cases the glands only were affected—i.e., there was no tubercle found in any other part of the body. In these cases the glands had become calcified, but in the others the structure and degeneration of the glands were tubercular, bacilli were very few in number and in some cases could

not be demonstrated, and the nature of the mass could only be determined by inoculation experiments. Here, again, the second and third periods account for more than all the others together, 5 and 4 from one to two and a half years and from three to five and a half years, against 5 for the other four periods (1 under one year; 1 between six and seven and a half years; 2 from eight to ten years; and 1 from eleven to fifteen years). These 14 cases were accompanied by neither ulceration nor cicatrization of the intestine; there was no peritonitis, and secondary tubercle could be found in no other parts of the body, so that the tuberculosis of the mesenteric glands must be looked upon as the primary lesion. Continuing the analysis, it was found that in this 100 cases the glands at the root of the lung are simultaneously affected in 69 cases, and in 62 the lungs were also affected; in 13 there was tubercular peritonitis, and in 18 ulceration of the intestine was also found. Of the remaining cases, 4 had tubercular peritonitis and 4 ulceration of the intestine. In 12 cases the mesenteric and mediastinal glands, the peritoneum, the intestine, and the lungs were all affected; whilst in no fewer than 53 of the 100 cases there was evidence of localised peritonitis, recent or old, occurring between the spleen or liver and the diaphragm. Of the whole 100 cases, only 20 were diagnosed as having abdominal tubercle, and this 20 would be considerably reduced were the doubtful diagnoses eliminated. In these cases, then, the symptoms associated with tubercle in other organs are so predominant that the tubercle in the abdomen was practically overlooked. Dr. Goodhart, speaking of this condition, says: "Caseous or tubercular disease of the mesenteric glands is not uncommon; nevertheless, it is rare indeed in comparison with the consumption of the bowels which is so often heard of in the dwellings of the poor. From a large out-patient department of the Evelina Hospital during several years, and when at least 6000 or 7000 children must have come under observation, and probably considerably more, I have only notes of 46 cases, and half of these were but of doubtful nature. Some few others are to be associated with phthisis, but as a substantive ailment we might have supposed it to be more common than it is." And Professor Gairdner, in his *Lectures to Practitioners*, draws attention to the fact that as pathological descriptions can deal with fatal cases only, a far too grave prognosis is arrived at in cases of tabes, and that consequently many cases of tubercular disease, not only of the mesenteric glands, but also of the peritoneum, recover, only the more grave cases succumbing. It is evident from all this that tubercular conditions of the abdomen are much more common than can be inferred even from the figures above quoted, where only one-fifth of the real number are stated in the diagnosis charts to be suffering from abdominal tubercle. That there is a great tendency towards calcification and cicatrization, especially where the tissues have a high resistant power, is well known to all pathologists, who constantly find cicatrices which are to be recognised as of tubercular origin (by the presence of small caseous or calcareous nodules, &c.), in which, however, the tubercle has become quiescent. These are the result of local tubercular changes, the localisation being due to the activity of the tissues.

In the Registrar-General's Supplement, 1871-80, a most interesting summary is given of the deaths from tubercular diseases. The death-rate from phthisis in the years 1851-60 was 1305 per million; from tabes mesenterica and scrofula, 1920. In 1861-70 the figures are 968 for phthisis, 2213 for hydrocephalus and tubercular meningitis, and 2267 for tabes mesenterica and scrofula; whilst in 1871-80 the figures are 767, 1800, and 2550. The differences in the proportions between these figures in the various years might be due in part to more accurate diagnosis, but in part they are to be accounted for by the increase in the death-rate from tabes. Including, as these cases do, the diagnosis of physicians both skilled and unskilled, it would appear from the results of post-mortem examination of the cases described that the last group might safely be multiplied by five to give the actual number of cases in which the mesenteric glands were affected, giving no less than 12·75 per 1000 as the rate of disease. If, in addition, those cases are taken in which the tubercular is followed by a reparative process, the numbers must be enormously greater.

It had already been noted that the maximum affection by mesenteric tubercle is attained between one and five years, whilst in tubercular meningitis the maximum is attained

between three and seven, amongst the cases of tubercular meningitis being included, of course, those cases in which there is also mesenteric tubercle. This fact, taken in connexion with the very large percentage of all tubercular cases (in children) in which mesenteric disease is developed, points very decidedly to the supposition that in these tubercular glands is the primary lesion in the body. Further, on examination of the statistics of these cases it is found that in 69 of the 100 cases of mesenteric tubercle the glands at the roots of the lungs are tubercular (the glands at the root were tubercular in 27 cases in which the mesenteric glands were not affected); but in by far the larger proportion of these cases, the tubercle in the lung is of more recent growth—i.e., caseation and calcification are not so frequently met with. On the other hand, taking the cases of lung tubercle altogether, it is found that the proportion of cases of early tubercle (catarrhal pneumonic and grey miliary or racemose tubercle) to older caseous tubercles or where cavities are formed, is as 36·3 to 63·7 per cent.

In what way can the causation of mesenteric tubercle in children at these ages be explained? In the class from which the patients in the Royal Hospital for Sick Children are drawn, the infants are during the first year of life, and sometimes longer, suckled at the breast, but afterwards the diet is extremely mixed; as a rule it is very unsuitable, but of course it is almost invariably partially composed of milk. It is after this first year that there is such a rapid rise in the number of cases in which the mesenteric glands are affected.

Although tubercle in the human subject is so frequently met with in young married women, tubercular mammitis is extremely rare; eight cases have, however, been collected and recorded by Dr. O. Hubermaas.¹ In cattle, on the other hand, where the mammary gland carries on its functions under conditions which are far from healthy, or at any rate far from normal, tuberculosis is not by any means of rare occurrence. The first experiments from which actual proof of the infective nature of tubercular material was obtained were performed by Gerlach, who used the milk of tuberculous cows as the material with which he fed young animals. His results were not all positive, but he was successful in a sufficient number to justify his conclusion that there was some specific virus in the milk of tuberculous cows, which would when ingested produce tuberculosis of the alimentary tract or mesenteric glands. Albert then recorded the case of a litter of young pigs, which were fed on the rejected milk from a tuberculous cow, the whole of the animals succumbing to tuberculosis.

Numerous other observers—Klebs, Bollinger, Stein, Johne, Bang, Toussaint, Chauveau, and many others, besides Koch—concur in stating that if milk from cattle with tubercular udders be given for any lengthened period tuberculosis will be developed. At the International Medical Congress in Copenhagen, Bang gave the results of an examination of no fewer than 27 cases of tubercular mammitis, and he was able to demonstrate the presence of tubercle bacilli in the milk or in the sediment, and with this milk or sediment he was able to produce tuberculosis both by inoculation and by ingestion. Nocard was able to demonstrate the presence of the specific bacillus in milk in 11 cases.

The lecturer then gave an account of a most careful and systematic examination of over 600 cows in the Edinburgh dairies, which he, along with Professor McFadyean, had carried out. Of the whole, they found 37 beasts in which there was mammitis, but only 6, or 16 per cent., in the milk of which they could demonstrate the presence of tubercle bacilli, and then only in small numbers. In 1 of the 6 cases, and subsequently in 5 other cases, they made sure of the existence of the bacilli in enormous numbers in the udder by microscopic examination. They find that new tubercular tissue is disseminated in patches of various sizes throughout a portion of the gland, and that all the more minute elements of tubercle may be distinguished—the small round cells in which the nuclei are comparatively large, and the epithelioid cells, between or amongst which is a fairly well developed reticulum. The giant cells are very numerous, but are not so well defined as one sees them in the human subject; they are scattered throughout the new tissue. The tendency to caseation of tubercle in the udder is not nearly so well

¹ Beiträge zur Klin. Chir. Mitth. aus der chir. Klinik zu Tübingen Band ii., Heft 2.

marked as in other parts of the body, but it does undoubtedly occur at points. The new growth of tuberculous tissue gradually invades the lobules of the gland, passing in along the lines of the lymphatics of the interlobular septa, so that a gradual transition from the healthy gland substance to the dense tubercular mass may be seen. In the mass itself the characteristic bacilli are present in almost inconceivable numbers. They are seen first as small stained rings (masses of bacilli) around a slightly granular or homogeneous mass—in fact, the giant cells seem to consist of the debris of cells, the result of the activity of the bacilli. In the smaller cells bacilli may also be seen, and others may be demonstrated lying in the spaces between the cells. On careful examination of the more healthy parts of the gland, especially at the margin of the new growth, ulceration into the ducts may be made out. In consequence of the interference with the nutrition of the tissues immediately around the ducts or acini, the basement membrane has given way and a small mass of tubercular granulation may be seen projecting into the lumen; the epithelium is also proliferating. In the granulation tissue, in the epithelial cells, and even lying free in the lumen, there are frequently numerous bacilli, and it can be easily understood how, once in this position, they find their way into the milk. This ulceration is not, however, of such frequent occurrence as might be expected, for in the greater part of the gland substance left there is little or no catarrhal proliferation, and the ducts and acini appear to be obliterated in great measure by compression. The lecturer pointed out that in connexion with this it would suggest itself to most of those who examined carefully the sections exhibited that what are called giant cells may in reality be nothing more than acini or ducts in which the bacilli have attacked and destroyed the epithelium. This idea would be greatly strengthened if some of the larger ducts were examined, for in these similar degenerative changes of the epithelium could be seen; in this epithelium bacilli could be demonstrated, and in the lumen itself there are frequently similar granular or homogenous masses in which a few bacilli may be seen. In addition to these positions, bacilli could be demonstrated in epithelial cells still attached, and also in rare cases in those lying free in the apparently healthy milk ducts, in which position Professor McFadyean had first demonstrated them. These facts, when considered along with the occurrence of bacilli in milk, with the feeding experiments recorded by so many observers, and the great prevalence of tubercle in certain classes of animals, go far to prove, he thought, that milk is a source of tubercular infection, especially to young children. He referred to the cases constantly cropping up in which pigs on dairy farms are affected with tuberculosis of a most typical character, and mentioned an outbreak (amongst pigs) on a dairy farm which could be distinctly traced to the milk of three cows in which the udders were markedly affected. It is a curious and significant fact, he observed, that all veterinary authorities concur in stating that cattle and swine are the two species in which genuine tuberculosis most frequently occurs. When it is remembered that on all dairy farms, and even on farms where pedigree cattle (cattle which are very frequently highly tubercular) are reared, the milk, especially that of cows suspected of disease, is given to the pigs, which often become tuberculous, it will appear in the light of recent researches that the disease is *propter hoc* rather than, as so many still hold, merely *post hoc*. It has often been objected, of course, that, if all tuberculous cattle gave tubercular milk, the human race would run a risk of being rapidly exterminated; but it might now be maintained, as the result of most careful clinical observation, that it is only when the functions of the intestine are interfered with, and when, in consequence, there are temporary or permanent alterations in structure and in the chemical constituents of the fluids and gas in the alimentary canal, that tubercle bacilli can make their way unaltered through the epithelial barrier. The importance of Koch's experiments on anthrax and cholera bacilli, when ingested, cannot be over-estimated, and most of those who have followed him in this line of experimentation have come to the same conclusions on this point, however widely they may differ on others. It is not only the intestine itself, however, that is affected by these functional disorders. The mesenteric glands are also placed at a great disadvantage. This may be easily understood when it is remembered how the slightest irritation in any position is almost immediately followed by changes in the lymphatic channels

and glands. Everyone is familiar with the peculiar condition of enlargement, congestion, and succulence that is found in such glands. This condition must be looked upon as the result of stimulation; the cells are roused into greater activity, they proliferate more rapidly, and take up the foreign matter; the gland as a whole acting as a kind of vital sieve. In this process, however, the store of resistant energy, if such a term might be used, is gradually diminished, and should tubercle bacilli find their way into the gland during or shortly after this extra stimulation, they run less risk of being destroyed by active epithelioid and lymph cells than when these cells are not already partially exhausted. This is true in greater degree only in the glands than in the other tissues. Everyone engaged in practice could recall the numerous cases in which tubercular disease of bone, of synovial membranes, &c., has followed on measles, scarlatina, small-pox, and similar conditions, or in which an attack of typhoid or intestinal mischief of some form had been looked upon as marking the date, soon after which serious tubercular mischief was developed. All this should be considered, leaving out of account the fact that healthy glands might find it difficult to cope with any large number of bacilli finding their way through the unhealthy surface. It should be borne in mind, also, that during the growth of the individual these glands are, under normal conditions, called upon to do much more work than during later life, owing to the fact that in the building-up process in the body there is excess of nutritive material required for the tissues, in consequence of which the secondary digestive function, which the lymphatic system performs, is severely taxed. Under normal conditions this is provided for, but in imperfectly and badly nourished children this is not the case. In the first instance, then, the glands act as vital filters, but, should the stimulation be too great, there comes a period at which they are destroyed; they degenerate, and may become encapsuled in fibrous tissue, or they may suppurate and so become foci from which other areas are affected. Where this sequence is preserved there is a still further danger at the second stage. So long as the gland is active, the irritant material passed along to it is so modified that it is removed almost inert, but as soon as the degeneration sets in the area connected with that gland is much more liable to ulceration, especially in the case of children.

As regards the identity of the bacillus tuberculosis in man and cattle, the lecturer said that he felt compelled to arrive at a conclusion directly at variance with that of Klein, and in accordance with that of Koch, Bland Sutton, Watson Cheyne, and numerous other workers, that any differences there may be between the size, manner of growth, and position of human and bovine tubercle bacilli are not sufficient to constitute a specific or even a varietal difference. As a matter of fact, these differences he found it impossible to detect, and stated that he had observed quite as great differences in size between the bacilli under the same cover glass from sputa of a phthisical patient as he had been able to detect between those taken from a cow and those from the human subject. In confirmation of this he handed round photographs, placed at his disposal by Drs. Troup and Edington, of bacilli in sputa, in which it could be seen that some are at least one-third, or even one-half larger than others (just the proportions mentioned by Klein). As regards position, he directed attention to the specimen of tuberculous udder (microscopic), in which were tubercle bacilli, some embedded in epithelial cells, and others lying singly in the spaces between the cells. The only point on which he could agree with Klein was as regards the granularity, and this he believed could be accounted for, not by any specific difference, but rather by the temperature at which the two forms are developed.

Klein's experiments and observations, by which he proved that fowls may be successfully inoculated with tubercle taken from a human subject, that in the same way one can inoculate from a guinea-pig to a cow, but that when it is attempted to inoculate from a cow to fowls the results are negative, were then spoken of, and in connexion with this Koch's statistics concerning the temperature at which tubercle bacilli can be successfully cultivated were quoted. Koch states that between 86° and 105° F. tubercle bacilli grow, but that outside these limits it is exceedingly difficult to obtain a luxuriant growth. If, then, the power of growth, the activity, and virulence of bacilli can be, even to a slight extent, modified by altering the temperature when they are growing outside the body, is it not probable that they may be equally modified within the body? and when it is

remembered that in the cow and pig the temperature is from 101° to 102° , in the calf 103° , in the horse 101° , and in the hen 104° to 105° , it could be readily understood that a very slight rise in temperature in these animals might modify very considerably the power of propagation, and indirectly also the virulence of the bacilli. He did not think either that Klein's statement, that "it is not experimentally proved that human beings can contract human tuberculosis by feeding on milk and flesh derived from tuberculous animals," could be backed by clinical experience and pathological evidence, both of which appear to be greatly in favour of the identity of the virus in the two subjects. It is of course impossible to bring direct experimental proof to bear in the case of the human subject, but the indirect evidence recently adduced by various continental observers and the examination of series of cases, such as those to-day brought forward, should be very strong evidence indeed that in children, especially in those who are subject to the wretched hygienic treatment and bad feeding to which unfortunately so many of our poorer-class children are exposed, tuberculosis may be contracted as the result of the ingestion of milk from tuberculous udders.

Some of the difficulties which at present stand in the way of dealing in any adequate manner with tuberculous cattle were then mentioned and commented upon. It was well known among cattle breeders that in many cases the animals may be in an advanced stage of tuberculosis and still be what they call "prime fat." When making the observations on tubercular mammitis, Professor McFadyean and he had found that the udder might be tuberculous (proved by microscopic examinations) without the slightest falling off in the general condition of the animal. It was also found to be an exceedingly difficult matter to determine whether they were dealing with a simple or a tubercular mammitis. In some instances they were aided by a consideration of the history of the disease; but very frequently, on the other hand, no history was to be obtained, the animals being brought in shortly after calving for the sake of their milk supply, and coming from all parts of the country, from Denmark, and elsewhere. In spite of what Bang and others had taught, they found that the only reliable method of detecting the tuberculous disease was by staining specimens of milk for the tubercle bacilli. Then, too, it was an exceedingly difficult matter to control the treatment during the life of the cattle which are to give our milk supply. From Denmark alone, in which country the veterinary profession has demonstrated the extreme frequency of tuberculosis in cattle, and where tuberculosis of the udder was first thoroughly described and the presence of tubercle bacilli in milk first systematically demonstrated, we get no less than one million pounds sterling worth of cattle annually, and from Hamburg and other ports we also derive a considerable number of cattle which, in coming to this country, especially in stormy weather, battered down in the badly ventilated hold of a steamer, are undoubtedly in some cases infected by a few tuberculous animals in the cargo. In Copenhagen the late Professor Panum, Herr Bille (formerly Danish Minister in America), and Dr. Borch considered the matter of the milk supply so important that they allowed themselves to be appointed a Committee of Control to the Copenhagen Milk-supply Company. This committee shortly after last February declared, with Professor Bang, that tuberculosis of the udder is not difficult of detection, and that a diagnosis can be made at a very early stage of the disease, as it presents so many marked characteristics. From the experience as above stated, the lecturer would be somewhat inclined to doubt this statement, more especially as Bang, in a paper on "Tuberculosis in Domestic Animals," read before the Copenhagen Medical Society on Feb. 28th last, stated that the milk from cattle affected with pulmonary phthisis contained bacilli, even when the udder was not in any way affected. Unless the udder was examined most carefully after death, there could be no proof of this. It was pointed out that the development of the disease in the udder is extremely rapid, and that an early diagnosis is imperative if the great danger that would arise from mixing the milk from affected cows with the milk of healthy cattle is to be avoided. In consequence of this report the Control Committee advised the directors of the Milk-supply Company to order a fortnightly examination by a veterinary surgeon of all cows supplying milk to their company; this examination to include a most careful inspection for tuberculous udders. When will some such course be adopted in this country?

ABSTRACT OF THE Croonian Lectures

ON

ANTIPYRETICS.

Delivered at the Royal College of Physicians,

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LECTURE IV.

IN the cases of typhoid fever investigated with so much care by Riess, the effect of antipyrin had been to diminish the total excretion of nitrogen from 15 to 30 per cent. Müller reported a case in which the urinary nitrogen was diminished by 28 per cent. on days when the pyrexia was suppressed by antipyrin, as compared with alternating days when it was allowed to rise unchecked. Engel, again, found the diminution, in similar circumstances, to be from 16 to 25 per cent. The agreement in these and other similar results appeared to establish the fact that in typhoid at least antipyrin exercised a constant influence in diminishing the metabolism of the nitrogenous tissues. It might be argued that the effect was not primary, but simply followed the lowering of febrile temperature. Umbach and others had accordingly made careful estimations of the effect of the drug on persons in health. By adopting a uniform diet for many days together Umbach brought about in himself a condition of nitrogenous equilibrium, and then took full doses of antipyrin on certain days. One series of observations extended over fourteen days, another over six days. The results were accordant, and showed that on the antipyrin days the nitrogen excreted was less by some 10 per cent. than on the normal days. This was due to diminished production of nitrogenous waste, not to retention, for on the days following the use of the drug the excretion gained its ordinary level and no more. There was thus good ground for the belief that in fever the lowering of temperature was a secondary phenomenon, the lowering of nitrogenous excretion a primary one.

The effect of antipyrin on perspiration was next considered. Too much importance had probably been attributed to the production of sweating as a thermolytic process in discussions in fever and its treatment. Profuse sweating was compatible with high temperature, as was seen in rheumatic and septicæmic fevers. The absence of sweating did not necessarily result in pyrexia from heat retention. The high temperature of fever was not reduced appreciably when the injection of pilocarpine gave rise to abundant sweating; sometimes it actually rose. Though in many cases antipyrin was followed by sweating, this did not sufficiently explain its cooling effect. Sometimes the sweating did not appear; it could be artificially suppressed by the simultaneous administration of atropine, yet the temperature fell notwithstanding. In certain cases of phthisis with colliquative sweating, the lecturer had seen antipyrin lower the hectic temperature and at the same time check the sweats, to the great comfort of the patients. Moreover, if the temperature of a fever patient be taken continuously, or at intervals of ten or fifteen minutes, it is occasionally observed that the fall of temperature begins before the perspiration appears.

Turning to the effect of the drug on the circulation, the lecturer recalled Dr. Wood's observation, that its thermal effect was independent of any measurable effect on the circulation. Denme of Berne, one of the first inquirers into the physiological action of antipyrin, stated that when very large doses were administered to animals, doses very much greater in proportion than any used in therapeutics, the first effect was to raise the blood pressure, the second to lower it. Ultimately the heart showed signs of paralysis, and then another dose of antipyrin failed to raise the pressure again. On the isolated heart, antipyrin, circulating with the blood in full doses, produced the effect of relaxation or paralysis; but if pure blood, or blood containing caffeine, were sent through it, the heart recovered per-