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OPHTHALMIC SURGEON TO THE KING EDWARD MEMORIAL HOSPITAL AT EALING AND TO THE QUEEN'S HOSPITAL FOR CHILDREN.

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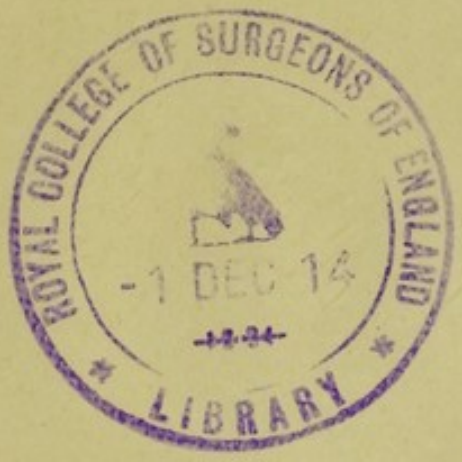

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TUBERCULOSIS OF THE EYE.*

NOT so very long ago tuberculosis was regarded as a rare cause of diseases of the eye. The text-books current in my student days had little to say upon the subject. The etiological importance of tubercle was then altogether overshadowed by that of syphilis.

Villemin's classic discovery that tubercle could be inoculated into rabbits (1865) was in 1867 applied by Langhans to the conjunctiva of those animals. The first definite case of tubercle of the human conjunctiva was brought forward by Koester in 1873, and was speedily followed by communications by Sattler, Walb, and others. In 1882 Pfeiffer published a paper on the bacillus tuberculosis as found in lupus of the conjunctiva. But so infrequent was the condition thought that, writing in the year 1885, P. H. Mules estimated the incidence of the disease at 1 in 33,000 eye patients. With this it is instructive to contrast the more modern estimates of 1 in 2700 (Eyre), 1 in 1660 (Saemisch), or 1 in 1000 (Stephenson).

For a knowledge of the fact that the lacrymal sac may be affected by tubercle we are indebted to the Zürich School of Ophthalmology, as represented by Haab (1879) and Amiet (1887). Pioneers were Wagenmann (1888), Leidholdt (1889), Fick (1890), and Bock (1891). In 1894 Jaulin devoted his Paris thesis to the subject. Among 52 lacrymal sacs excised in Wagenmann's clinic, Grobe and Hertel found tuberculous changes in 7 per cent., while Rollet found the same lesions in 8 per cent. of 46 extirpations. In May, 1910, an important discussion

* Remarks preliminary to a demonstration of cases of tuberculous disease of the eye given at the Medical Graduates' College and Polyclinic, London, on Oct. 24th, 1913.

(opened by E. Rollet) on tuberculosis of the lacrymal passages took place at the French Ophthalmological Society.

Interstitial keratitis was described by the famous William Mackenzie in 1830 as "scrofulous corneitis," but in 1863 Sir Jonathan Hutchinson showed that the affection was almost always a direct result of inherited syphilis. The influence of acquired syphilis in that direction was not then recognised by Hutchinson. To some extent professional opinion has now veered round to Mackenzie's view. It is known that some of the cases, particularly the unilateral and less typical ones, are due to tubercle. For example, in my own series of 101 cases of interstitial keratitis[1] tuberculosis was identified as the cause in 9·90 per cent. In short, the modern biological tests for tuberculosis have supported the view, originally based on clinical observation, that tubercle is a cause of primary keratitis.

Conditions that we should now regard as tuberculosis of the iris were described by Lawrence in 1833 and by Mackenzie in 1854. Such cases were examined with the microscope by Richetti in 1869 and by Berthold a couple of years later. In 1890 Julius von Michel[2] stoutly maintained that inflammation of the iris due to tubercle was nearly as common as that due to syphilis. Iritis might result from tuberculous infection, and yet might not be accompanied by tubercles. Michel held that a tuberculous inflammation of the iris might be the first visible expression of tubercle in some other part of the body.

The foregoing views received support from the experimental work of W. Stock,[3] who by the injection of pure cultures of tubercle bacilli into the auricular vein of rabbits was able to produce inflammation of the iris and ciliary body (anterior uvea), to say nothing of other structures of the eye, such as the cornea, the sclera, the choroid, the conjunctiva, and the tarsus. The naked-eye characters of these experimental inflammations in many instances did not conform with those generally regarded as characteristic of tubercle, neither did their histological structure, despite the all-important fact that tubercle bacilli could be found in them.

That tubercles might form in the choroid has been known since G. de Mussy found them after death in 1837, Jaeger recognised them during life with the ophthalmoscope in 1855, and Manz examined them with the microscope in 1858. In 1896[4] I described a chronic form of choroidal tubercle, of which I had seen examples in the fundi of "strumous" children, and I adduced reasons for believing that such lesions might become absorbed, leaving behind them more or less characteristic changes in the fundus oculi. Some few years afterwards the late George Carpenter and myself[5] again described these deposits as instances of "obsolescent tubercle," and in reference to acute miliary tubercle of the choroid, estimated that those changes were found in at least 50 per cent. of cases of tuberculous meningitis. Various choroidal lesions believed to be of a tuberculous nature were found in 11 of 119 patients suffering from such various forms of surgical tuberculosis as adenitis, enlarged joints, spinal caries, and chronic tuberculous cerebral tumour. Recently, Wilbur B. Marple,[6] working at the Babies' Hospital, New York, found miliary tubercle of the choroid in 13 consecutive cases of tuberculous meningitis (100 per cent.). The examinations were made at very frequent intervals, the electric ophthalmoscope being used for the purpose.

Material support to the present writer's views on the subject of "obsolescent tubercle" has been given by T. Harrison Butler,[7] who saw eight such cases among 5000 eye patients. In some of his cases the tuberculous nature of the cases was demonstrated by the employment of tuberculin. Carl Koller,[8] of New York, too, has reported two of these cases, which presented so definite a clinical picture that Koller claimed it as "one of the ophthalmoscopically recognisable forms of choroiditis." In one of his cases, after the injection of tuberculin, Koller obtained reaction in the affected eye, as shown by opacities of the vitreous and change in the colour of the choroiditic lesions.

Despite the dictum of Calderaro,[9] that tubercle of the sclera is primitive, and that even when associated with other tuberculous manifestations, probably arises from exogenous infection, it is likely

that the condition in question is nearly always secondary to tubercle of the anterior uvea. The dense fibrous tissue of the sclera would naturally be inimical to the implantation and the development of the virus. Inspection of a section of tuberculosis of the uvea sometimes gives the clue to the origin of tuberculous scleritis. It shows collections of lymphoid and endothelioid cells lodged in the close neighbourhood of vessels in the thickness of the sclera, but separated by sound tissue from the ciliary body, on the one hand, and the surface of the sclera, on the other, although at the same time a nodule of typically tuberculous tissue may be found in the latter position. The transference in this case has been by metastasis. There is another and perhaps commoner mode of origin from the anterior uvea—namely, by direct spread. As surmised by Hancock and Mayou,[10] many cases of tuberculous scleritis doubtless masquerade as instances of episcleritis.

From what has been said it will be evident that the tubercle bacillus is becoming more and more widely recognised as a cause of diseases of the eye. It is now known that every part of the eye and its appendages, with the single exception of the crystalline lens, may be invaded. By almost universal consent, the B. tuberculosis is now ranked next in importance only to the spirochæta pallida as an etiological factor in maladies of the eye. Apart from such paratuberculous conditions as phlyctenulosis I must not be understood as claiming that tuberculous affections of the eye are common. That would be far from accurate. But we know that tubercle affects structures of the eye once believed to be exempt, while some tuberculous maladies, formerly believed to be very rare, are now known to be comparatively frequent. In other words, tubercle of the eye is relatively but not absolutely common. It need hardly be said that a tuberculous condition of the eye implies the existence of tubercle bacilli, human or bovine, and that these may gain entrance to the eye either by exogenous or endogenous infection.

Such conditions as tubercle of the conjunctiva or of the lacrymal sac appear to be nearly always due to exogenous infection. To the conjunctiva the

bacillus gains entrance by a scratch, an abrasion, a broken-down phlyctenule, a penetrating wound (accidental or surgical), or even, as suggested by John W. H. Eyre,[11] between the interstices of the epithelial cells of an apparently normal conjunctiva. On the other hand, tuberculosis of the inner parts of the eye, as the iris, ciliary body, or choroid, are nearly as invariably the outcome of endogenous infection carried by the blood stream from a focus of tubercle in some other part of the body to the eye.

While such is, broadly speaking, the etiology of the conditions named, exceptions of course occur. On two occasions W. Stock,[3] whose work has already been alluded to in this communication, succeeded in producing tubercle of the conjunctiva by injecting cultures of tubercle bacilli into the venous system of the rabbit. This will prepare us for the statement that on occasion tubercle of the conjunctiva may be due not to exogenous infection, as is the rule, but to endogenous infection. This happened in a case reported by myself[12] some years ago, where a female child, aged 17 months, suffered from tubercle of the conjunctiva as part of a generalised tuberculosis, with pulmonary, meningeal, and choroidal manifestations. The case was fatal. In a somewhat similar sort of way tuberculosis of the iris has been known to follow a wound (E. Fuchs, L. Dor).

The distinction between the two kinds of infection, exogenous and endogenous, is not without practical importance. For example, an exogenous lesion, such as a tuberculous lacrymal sac, may be completely removed, and all chance of generalisation be thereby abrogated. On the other hand, it would be of little use removing an eye with tubercle of the iris or choroid with a view to prevent generalisation, since the condition practically always originates from a tuberculous lesion elsewhere. Yet it is not so many years ago that a deservedly popular text-book on diseases of the eye recommended that way of dealing with tuberculous iritis. It is quite a different thing when removal of such an eye is rendered necessary by the local conditions, especially by pain, although Rogman[12] and others have drawn attention to the danger

attendant upon enucleation in tuberculosis of the eyeball.

Some tuberculous maladies of the eye are so characteristic that they may be recognised as such almost literally at a glance, but there are many more that cannot be diagnosed in that simple way. In dealing with an accessible lesion—for example, a diseased lacrymal sac—we first try to find the specific micro-organism in the pus after the latter has been mixed with antiformin, or that failing, we seek for it in excised granulations. A simple method I have sometimes employed with success is to wash a bit of excised tissue free from blood in several changes of sterile water, and then, after cutting it open with knife or scissors, to smear several cover-glasses with the raw surface. The prepared glasses are stained in the ordinary way with carbol-fuchsin. This method of diagnosis may be applied also to a conjunctival granulation or to a diseased nodule excised from the sclera. Only in case of failure does it become necessary to resort to emulsification, the centrifuge, and other methods, into which it is not my intention to enter now. If Koch's bacillus be found under the circumstances we may safely conclude that the condition is of tuberculous nature.

In some circumstances we turn to the histological diagnosis, particularly when the conjunctiva is affected. A morsel of affected tissue is excised with scissors, hardened in formol, and cut in paraffin. The sections are then stained for structure (hæmatoxylin-eosin) and for acid-fast bacilli (Ziehl-Neelsen method). Such specimens from the conjunctiva frequently show the most beautiful pictures of tuberculosis, including giant cells of the Langhans type and areas of caseation. Indeed, complete tubercle-systems are common. It is unfortunate that the histological diagnosis is apt to fail us in what is clinically the most common form of conjunctival tuberculosis—namely, that characterised by hypertrophic granulations, the so-called "cockscomb excrescence." Sections from such cases usually show little more than so many lymphocytes, together with small blood-vessels embedded in scanty connective tissue. Moreover, in cases which represent extension of lupus from the skin to the

conjunctiva the histological investigation seldom yields conclusive results. In these two forms of conjunctival tuberculosis, as pointed out by John W. H. Eyre,[11] the tubercle bacillus is difficult to find. It was formerly thought that Müller's fluid, then employed almost to the exclusion of other fixatives in eye specimens, was responsible for the difficulty. But the fact that Haab[14] succeeded in demonstrating the bacilli in specimens that had lain in Müller's fluid for several years speaks against the view. It is much more likely that the organisms are hard to find simply because they are present in extremely small numbers, a respect in which we are reminded of lupus vulgaris.

Prominence has recently been given to the work of G. Liebermeister,[15] who holds that atypical anatomical lesions may result from the action of the tubercle bacillus. He found that guinea-pigs inoculated with such atypical products became infected with tuberculosis. In other words, Koch's bacillus need not of necessity produce a histological tubercle, although that is its most characteristic product. W. Stock[3] found that the ocular lesions experimentally brought about by injection of tubercle bacilli into the blood of rabbits often failed to show a typically tuberculous structure, although the B. tuberculosis could be demonstrated in them. In my own experience, this is sometimes seen in sections from human tuberculous uveitis, where the sole histological evidence of tubercle is furnished by scattered nodules of lymphocytes, and yet on other grounds, notably the finding the tubercle bacillus, it cannot be doubted that the lesion is tuberculous. In the choroid, on the contrary, the lesion is generally of the most distinctive type. The tubercle, whether submiliary, miliary, or massed, is a typical histological tubercle. The anatomical changes in tuberculous lacrymal sacs, again, are often of a highly characteristic nature. In reference to this point Bribak[16] insists that the whole sac should be cut in series, since otherwise a small tuberculous deposit may be readily overlooked. Fibrosis, which involves much thickening of the wall, is regarded by Collins and Mayou[17] as characteristic of the condition. Sections of tuberculous scleritis, while they seldom include many tubercle bacilli, usually show

typical giant cell systems, together with caseation. In this country we are precluded from a resort to the most certain of all tests—viz., the inoculation of suspect material into an animal susceptible of tuberculosis, such as the guinea-pig.

When dealing with an affection of the deeper parts of the eyeball suspected to be of tuberculous nature a method of diagnosis adopted by myself and some others may be employed. It consists in drawing off the aqueous humour and in examining it directly for tubercle bacilli, or in trying to cultivate those organisms from it, or in inoculating it into the eyes of experimental animals. Gourfein [18] was the first to employ this method. Soon after the publication of his first communication I succeeded in growing the tubercle bacillus on glycerine-agar inoculated with aqueous humour from a case of tuberculous uveitis. Another of my experiences was communicated to the Ophthalmological Society in October, 1907.[19] The facts follow. A female, aged 35 years, suffered from iridocyclitis of one eye. When the keratitic deposits had cleared enough to allow the fundus to be seen, what appeared to be a tubercle of the choroid was found near the optic disc. The anterior chamber was tapped, and careful examination of cover-slips smeared with the fluid led to the discovery of a few acid-fast bacilli. The patient (seen only the other day) is now in good general health, although she reacts strongly to von Pirquet's surface vaccination. The choroid shows an obsolescent tubercle. In yet another instance of chronic iridocyclitis,[20] where the clinical evidence of tubercle was slender and included only a slight rise in temperature towards night, increased pulse-rate, and one enlarged gland at the angle of the jaw on the left side, a restricted number of tubercle bacilli was found in the aqueous humour obtained after the affected eye had been enucleated. The presence of tubercle, however, had been attested in this patient, a girl aged 12 years, by the general reaction that on two occasions followed the subcutaneous injection of 1/1000 mgr. of tuberculin T.R., as well as by the focal reaction that was produced by applying Calmette tuberculin to the sound eye.

Lastly, we have at disposal other means for the recognition of deep-seated tuberculosis of the eyeball, as of other parts of the body. Leaving aside the biochemical examination of the blood serum with a view to the detection of specific antibodies, hypersensibility towards the toxins of tubercle may be demonstrated in several ways, of which two alone need be glanced at in this place—viz., (1) von Pirquet's skin reaction ; and (2) Koch's subcutaneous test.

1. Von Pirquet's skin reaction, as well known, merely consists in making three small vaccination marks upon the forearm (or elsewhere), and allowing a drop of 25 per cent. old tuberculin to act upon two of the scarifications, the third being left as a control. Hyperæmia of the marks treated with tuberculin within 24 hours of the little operation testifies to a positive reaction. At this stage the resemblance to a mosquito bite is often very close. The advantages of the von Pirquet method are that it is easily performed, is free from danger, and may be used in out-patients. On the other hand, the test is so sensitive and tubercle (past or present) is so common † that, except in young children, the reaction is not of much diagnostic use. Singularly enough, a negative reaction is of greater value than a positive. An eye disease suspected to be of tuberculous origin is certainly due to something else if the patient fails to react to the careful use of tuberculin. A drawback of the von Pirquet method from the present standpoint is that from it we obtain no reaction as regards the eye lesion, so that we are cut off from a valuable means of diagnosis. In other words, the plan can merely certify us that a tuberculous lesion (active or latent) is present in some part of the body, without indicating its locality.

2. These disadvantages do not apply to the Koch subcutaneous method, which in return has some peculiar to itself. The "general reaction," as

† Evidences of tuberculous infection were found by Hamburger in 77 per cent of the necropsies made on children dying between the ages of 11 and 14 years, and by Naegeli in no less than 97 per cent. of the bodies of adults.

everybody knows, is shown by a rise in temperature some few hours after the injection of old tuberculin into the subcutaneous tissue, reaching a maximum in about 12 hours, and then falling slowly to normal. The outstanding advantage of the method is that some appreciable change, as increased redness, is observed in perhaps one-half the cases in the affected eye, and this "focal reaction," as it is called, stamps the lesion in question as tuberculous. Upon one form of focal reaction great stress has been laid by W. Stock [3] as a sign positive of tuberculosis. This consists in tiny grey deposits or thickening of the iris in the minor circle of that membrane. Something of a similar kind has been described by G. Tobias [21] in the shape of fine greyish spots situated at different levels in the substance of the cornea. These, like the changes signalised by Stock, are scarcely likely to be identified without the help afforded by the binocular magnifying glass.

The great advantage of the Koch method may be more than counterbalanced by the fact that on occasion the focal reaction produced by the tuberculin may exceed the limits either desired or expected of it. For example, rapid extension of ulceration or grave diminution of vision has been known to follow the operation. The former accident was mentioned by John W. H. Eyre,[11] while the latter has been described by W. E. Gamble.[22] In Gamble's patients the injection of old tuberculin was followed by a reduction of sight from 20/40 to 20/100 in the one case, and from normal to less than 1/10 in the other. The failure of sight, which occurred simultaneously with the general reaction, began some 17 hours after the injection, and lasted for three days or longer. In a case of tubercle of the fundus reported by Kraus and Brückner [23] focal reaction following the injection of tuberculin manifested itself under the guise of an increased number of hæmorrhages and œdema of the retina. Edgar Chatterton [24] observed an intraocular hæmorrhage in a child with iridocyclitis in course of treatment by tuberculin, but was not altogether satisfied that the two were connected as cause and consequence. T. Harrison Butler [25] has on several occa-

sions seen the injection of tuberculin do harm. In one case of tuberculosis of the iris in a patient with a hectic temperature Butler gave 1/10,000 mgr. of T.R. after the temperature had been brought to normal by rest in bed. "The result," writes Butler, "was disastrous and hastened the inevitable loss of both eyes." He mentions two other cases where a condition of anaphylaxis had supervened, since in both tuberculin had been employed without mishap on former occasions. In the first, a severe example of scleritis of both eyes in an elderly woman, a relapse was treated with 1/5000 mgr. of T.R. As a result both eyes became violently inflamed and intractable iridocyclitis supervened. In the other case, of which no details are given, Butler states that the focal reaction caused considerable anxiety. The author as the result of his experience holds that a focal reaction obtained during a course of tuberculin treatment always does harm in eye cases, and on occasion great harm.

It would be impossible to conclude without paying a tribute to A. von Hippel,[26] who in 1904, at a time when tuberculin lay under a cloud, showed how it could be used successfully in cases of eye disease. He had employed it for ten years, and had come to regard it as a means of saving eyes that he would once have considered beyond medical help. He employed graduated doses of tuberculin T.R., and in serious cases continued the remedy for six months at least. Injections, carefully controlled by the bodily temperature, were given every second day. Treatment was commenced with 1/500 mgr., and the dose was increased by 1/50 mgr. up to 1/5 mgr., and then by 1/10 mgr. to 1 mgr., an amount that was not exceeded.

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