The Hunterian Lecture on tuberculosis of the conjunctiva : its etiology, pathology, and diagnosis / by John W. H. Eyre.

4

The Hunterian Lecture

ON

TUBERCULOSIS OF THE CONJUNCTIVA: ITS ETIOLOGY, PATHOLOGY, AND DIAGNOSIS

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BY

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TUBERCULOSIS OF THE CONJUNCTIVA: ITS ETIOLOGY, PATHOLOGY, AND DIAGNOSIS.

MR. PRESIDENT AND GENTLEMEN,—Tuberculosis of the conjunctiva may be shortly defined as an infective granuloma affecting the conjunctival tissues, whether bulbar or palpebral, due to the local multiplication of bacillus tuberculosis and to the action of the toxins it elaborates. Clinically its manifestations are protean; histologically its basis is the giant cell system, although in some instances the surrounding hyperæmic granulation tissue completely masks the fundamental "tubercle."

From this definition it follows that the presence of the tubercle bacillus is indispensable for the existence of tuberculosis of the conjunctiva, and a diagnosis based upon clinical data only, and not confirmed by the demonstration of the specific micro-organism, must be regarded as entirely foreign to the present thesis, since the clinical appearances may be simulated by conditions due to causes quite other than bacillus tuberculosis; whilst the histological characters, including the giant cell system, may be present in chronic lesions due to the activity of practically any micro-organism.

It is unnecessary, therefore, to do more than refer in passing to phlyctenular conjunctivitis, although owing to its occurrence in individuals of tender years, and of the "strumous" or "scrofulous" type, it has been regarded by many as tuberculous in character. That many of those subject to phlyctenules give evidence of the existence of tuberculous infection in some portion of their tissues is no evidence that the conjunctival lesion is also tuberculous, and until some responsible observer has demonstrated the presence of the tubercle bacillus in an extended series of phlyctenules I see no valid reason for regarding phlyctenular conjunctivitis, *per se*, as a form of tuberculosis of the conjunctiva. I rather regard phlyctenules as an expression of enfeebled vitality and

lowered cell resistance in an individual whose ocular system is habitually in a state of irritable tension (for practically every phlyctenule patient suffers from some error of refraction)—a combination which enables any micro-organism to provoke a reaction out of all proportion to its virulence. Similarly the clinical entity designated chalazion cannot be regarded as a form of conjunctival tuberculosis. It is true that Tangl demonstrated tubercle bacilli in tissue, histologically tuberculous in structure, which had been removed from one typical case of chalazion; but this was an isolated instance, and many other equally competent observers have sought in vain to repeat his observation. Despite, however, my disinclination to regard either the phlyctenule or the chalazion as primarily tuberculous, each on occasion may have assigned to it an important rôle in the causation of tuberculosis of the conjunctiva—that of serving as the portal of entry to the tubercle bacillus.

Historical Summary.

Since the early part of the nineteenth century various observers have recorded inflammatory new formations arising in the conjunctiva, and the descriptions, read in the light of our present-day knowledge, leave but little doubt as to the tuberculous nature of these granulomata. The earliest of these I have been able to trace is not yet a century old—the account by Lawrence (1833) in which he clearly describes [1] the fleshy granulations of tuberculous conjunctivitis so characteristic of the third of Sattler's groups or types. Somewhat later Mackenzie (1854) writes of conjunctival and sub-conjunctival tumours which he evidently regarded as tuberculous,[2] then nine or ten years elapsed before we find Arlt (1864) writing of lupus of the conjunctiva. Next came a period of inactivity so far as concerns clinical observations, but in this interval laboratory workers were far from idle. First came an exceedingly valuable contribution to the pathology of tuberculosis from Villemin (1865), who demonstrated upon rabbits the infectivity of tuberculous material. Applying this important discovery to his own sphere of research, Langhans (1867) soon demonstrated the experimental production, also in rabbits, of tuberculous infections of the conjunctiva—observations which he embodied in his inaugural dissertation at Marburg—at about the time Virchow was affirming the insusceptibility of the conjunctival membrane to tuberculosis. Now comes the first definite record of a case of tuberculosis of the human conjunctiva, communicated by Koester (1873), followed the next year by Sattler's

[1] "Sometimes innocent fungous excrescences arise from inflammation affecting the anterior part of the globe, ... a fleshy vascular substance may spring up from the surface of the sclerotic coat."

[2] "I have seen several cases of what seemed to be scrofulous tubercles."

contribution of a case of tuberculous ulceration of the conjunctiva, and a little later still by similar records by Walb and Hock (1875) respectively, and a further contribution on lupus of the conjunctiva by Alexander (1875).

Case after case was now published in rapid succession, but no good purpose can be served by enumerating them; indeed, they, like those which preceded them, are merely of academic and historic interest, since the diagnosis in every case was based upon clinical and histological evidence only. But in 1882 Koch published his memorable observations upon bacillus tuberculosis, and showed how its presence could be demonstrated in lesions resulting from infection of the tissues by this micro-organism. The importance of this discovery was immediately recognised and promptly applied to the investigation of diseases of the conjunctiva, for in the following year a paper appeared by Pfeiffer (1883) on tubercle bacillus in lupus of the conjunctiva, and two years later one by Ulrich on tuberculous conjunctivitis (1885) detailing the microscopical findings. Mention must also be made of a contribution which appeared by Parinaud (1884) on the diagnostic value of experimental inoculations into the anterior chamber of the rabbit's eye of the infected conjunctival tissue removed from cases of this disease. With these last-mentioned contributions to the subject the diagnosis of tuberculous conjunctivitis may be considered to have been placed upon a sound and scientific basis, and the only further reference of historic interest to which attention must be directed is the masterly paper some seven years latter in which Sattler (1891) for purely clinical purposes classified the various types of the disease according to the naked-eye appearances he had observed.

Case Incidence.

Figures dealing with the incidence of tuberculosis of the conjunctiva upon the entire population are not, so far as I am aware, available for any town, district, or country, but many ophthalmologists have recorded the total number of new cases that have come under their observation during some specified period, and also the number of cases they have diagnosed as tuberculosis of the conjunctiva, so that a simple calculation enables the ratio existing between the two classes to be determined. The frequency figure thus obtained varies enormously; thus, in round figures, one observer puts it at 1 in 1600, another at 1 in 30,000. I have previously reported frequency figures of 1 in 3000 and 1 in 2700, and have expressed the opinion that probably some cases have been overlooked. Although I see a number of cases of this disease, I am no longer in a position personally to calculate a frequency figure, but during the last five years 31,900 new

cases have passed through the ophthalmic department of Guy's Hospital and have yielded ten cases of tuberculosis of the conjunctiva, which gives a figure again of about 1 in 3200, but as many re-admissions are reckoned amongst these "new" cases I am of opinion that my previous figure of 1 : 2700 or even 1 : 2500 is approximately correct. The various recorded figures may be set out as follows :—

1881.	Hirschberg ...	1 : 17,000*	
	Horner	1 : 4000	
1882.	Milligan... ...	1 : 20,000	
1885.	Mules	1 : 33,000	
1889.	Spangenberg ...	1 : 17,000	
1897.	Eyre	1 : 3000	
1898.	Remlinger ...	1 : 1900	
	Bock	1 : 10,000	
1900.	Eyre	1 : 2700	
	Lagrange and Cabannes ...	1 : 7500	
1902.	Stephenson ...	1 : 1500	
1904.	Pegorora	1 : 13,500	
	Saemisch	1 : 1660	
1906.	Gourfein	1 : 1630	
1908.	Casali...	1 : 3200	
1912.	Ophthalmic Department, Guy's Hospital.	1 : 3200	

* Erroneously quoted on previous occasions as 1 : 6000. Hirschberg recorded three cases of *ocular* tuberculosis amongst 17,000 new patients, but of these three cases, one only was of tuberculosis of the conjunctiva.

Diagnosis.

In discussing the diagnosis of tuberculosis of the conjunctiva precisely the same methods are available that would be employed did the infective process occur in any other situation of the body. It will therefore be well to discuss these various methods seriatim under the headings of Clinical Methods and Laboratory Methods. Briefly, they are as follows :—

Clinical methods.—(*a*) Clinical examination of the local lesions presented by the patient ; (*b*) Clinical demonstrations of hypersensibility towards the toxins of bacillus tuberculosis.

Laboratory methods.—(*c*) Microscopical and bacteriological examination of the diseased conjunctiva with a view to the detection of B. tuberculosis. (*d*) Biochemical examination of the patient's blood serum with a view to the detection of specific *antibodies* to bacillus tuberculosis.

Clinical Methods.

(*a*) *Clinical Types and Differential Diagnosis.*

From the point of view of clinical diagnosis cases of tuberculosis of the conjunctiva can often be arranged in one or other of several distinct groups, and recognising this feature Sattler in 1891 summarised the characteristic features of each of several groups. These, with very slight modifications,

have formed the basis of the clinical classification which is in use at the present day. It must not be supposed, however, that every case of tuberculosis of the conjunctiva, typical though it may be in appearance, can be referred to any one or other group without some degree of hesitation, since it sometimes happens that two or even three of these clinical types may be noted as present upon different parts of the palpebral or bulbar conjunctiva of the same eye; but, on the other hand, one or other clinical formation usually preponderates to such an extent as to justify the classification of that case under one particular heading.

The clinical types of tuberculosis of the conjunctiva that are recognised to-day are five in number, and their relative frequency, as instanced in a series of cases that I have analysed for the purpose of this lecture, and in which the diagnosis has been placed beyond a shadow of doubt either by the recognition of the tubercle bacillus or by the positive result of an experimental inoculation, or by both these methods, is shown in the following table :—

Group I.—Ulceration	46
,, II.—Miliary tubercle	25
,, III.—Hypertrophic granulation...	80
,, IV.—Lupus...	46
,, V.—Pedunculated tumour	9

From this it would appear that the type most frequently met with is that classed under Group III., whilst Groups I. and IV. are the next most prominently represented types. I fancy, however, that the frequency of the lupus type of tuberculous conjunctivitis is more apparent than real, for, as it occurs in association with lupus of adjacent areas of skin or mucous membrane, it very rarely escapes detection, whilst other types sometimes acquire an incorrect diagnosis.

From a consideration of the cases that have come under my own notice and of recorded cases where descriptive details were available it is almost impossible to avoid the conclusion that the miliary tubercle, as met with in Group II., is the basis of all the clinical types—with perhaps the exception of Group IV. (lupus)—of tuberculosis of the conjunctiva, and that were the cases of any of these groups seen early enough the miliary tubercle would be the only manifestation of the disease. The subsequent differentiation of the primary lesion into the various clinical types is, in all probability, due to variations in the number of the bacilli introduced into the conjunctival tissue, or in the virulence of the virus, or, on the other hand, is an expression of the variation in the relative susceptibilities of the tissue cells of the infected individuals.

Arguing on these lines, I should regard cases of Group I. and III. as indicating the inoculation of distinctly susceptible individuals with numerous virulent bacilli, and cases of Groups II., and particularly V., as instances of infection of

resistant individuals with small numbers of attenuated bacilli.

Group 1., Tuberculous ulceration.—The symptoms of which the patient complains are often exceedingly slight, even when on examination extensive lesions are noted, but if any considerable induration and œdema of the lids exist there is severe pain; usually the symptoms consist of some slight photophobia and lacrymation, with little or no pain; sometimes the only symptom actually complained of is a muco-purulent discharge, which in the morning is found to have gummed the lids together.

The infection is commonly localised to the tarsal conjunctiva or to one or other fornix; and may involve the caruncle and plica semilunaris. In these situations there is sometimes relatively little inflammatory reaction in the surrounding tissues; on the other hand, there may be marked induration of the lid tissues, accompanied by hyperæmia and œdema. Less commonly the bulbar conjunctiva is affected, and when such is the case there is practically no inflammatory reaction in the lids, or in the adjacent tunics of the globe, and often, indeed, very little injection of the anterior conjunctival vessels. Ulceration is the chief feature of this group, at first in the form of small miliary ulcers of 1 to 2 millimetres in diameter, the edges sharp, serrated and slightly raised, the base uneven and greyish yellow from the presence of caseous slough. Adjacent ulcers may coalesce, and the extension of the process frequently leads to the formation of ulcers of considerable extent. In the vicinity of the ulcer or ulcers it is not uncommon to find small miliary tubercles, usually minute, sometimes slightly larger, 1 to 2 millimetres in diameter, in which case they resemble the tubercles subsequently to be described under Group II., and these no doubt play an important part in the extension of the process. In certain cases, often characterised by no very lengthy history, an extensive ulceration is found upon examination. In all the cases of this group the preauricular gland is involved. The gland is swollen, hard in the early stages, soon becoming caseous in its centre, and then soft and fluctuating, usually freely moveable over the deeper structures, and in the early stages at any rate not adherent to the skin above. In advanced cases further glands of the lymphatic chain are involved also—the gland at the angle of the jaw, the submaxillary and often the submental glands of the same side. Later still the deeper lying glands situated over the carotid vessels in the anterior triangle of the neck become infiltrated and hard.

The most important variety of conjunctival ulceration other than the tuberculous is the syphilitic. Here the comparatively rapid history, the pain, the brawny œdema of adjacent tissues, the sharp cut edge of the ulcer with its indurated sloughing base, the neighbouring adenitis (of the preauricular and submaxillary glands) are points of diagnostic importance. All,

however, sink into insignificance beside the microscopical demonstration of the spirochæta pallida in film preparations of the serum exuding from the ulcer, when Burri's Chinese ink method is employed. Less likely to be mistaken for tuberculous ulcerations are those due to epithelioma and rodent ulcer. The pustules of anthrax and vaccinia are also seen, although but very rarely, infecting the conjunctiva. Here the rapid onset, the clinical course, the history of exposure to infection, the severe malaise and elevation of temperature, assist in the diagnosis of the condition almost as much as the naked-eye appearances of the vesicles or pustules.

Group II., Miliary tubercles.—In this form subjective symptoms are absent, or are reduced to the complaint of trivial discomfort in the form of grit in the eye. Occasionally some lacrymation or dimness of vision, obviously due to lacrymation, is all that prompts the patient to seek advice; muco-purulent discharge is absent. The lesion is most frequently to be found upon the tarsal conjunctiva, less frequently on the bulbar conjunctiva, and when affecting this position is usually situated close to the corneal limbus on the equatorial line. Most rarely it occupies a linear position in one or other fornix. Objectively this group is characterised by the presence of greyish or yellowish or greyish-yellow nodules, which very closely resemble trachoma granules when grey, or the tubercles met with in the lungs of acute miliary tuberculosis when yellow is the prevailing tint. They are very frequently arranged in rows or aggregated into small groups. Sometimes they are more widely disseminated, but usually they only affect a small area or a narrow strip of the conjunctiva. They vary from 1 to 3 millimetres in diameter. Beyond slight injection of the neighbouring blood-vessels they cause no inflammatory reaction in the surrounding structures, and for a time at any rate they show but little inclination to undergo necrotic disintegration. Later the cornea may become involved and show a certain amount of pannus, in which are set small greyish-red nodules. These sometimes undergo necrosis, and give rise to definite ulceration of the cornea. The preauricular gland on the affected side is usually, but not invariably, involved.

The differential diagnosis here may have to be very carefully considered, as between tuberculosis and early trachoma, simple granular (follicular) conjunctivitis, ophthalmia nodosa, and Parinaud's conjunctivitis when affecting the palpebral conjunctiva, vernal catarrh and phlyctenular conjunctivitis when involving the bulbar conjunctiva, to say nothing of the small beginnings of lipoma, adenoma, and simple, parasitic and dermoid cysts. Leprosy may also involve the conjunctiva, when it is usually of the nodular type and extends to the tarsal conjunctiva from adjacent nodules on the skin surface. Glanders, too, may affect the conjunctiva, and may be suspiciously like the tubercles I have described. Usually, however, the lesion

is in the form of a small umbilicated vesicle, containing purulent material. It is a condition that I have seen once only, and then similar vesicles were present on other parts of the body and were associated with small subcutaneous glanders nodules.

Group III., Hypertrophic granulations.—In this and the following group the subjective symptoms are in general more marked than in the other three. Pain, photophobia, lacrymation, swollen œdematous eyelids, muco-purulent discharge, enlarged preauricular and submaxillary glands, are all symptoms of which the patient complains. The lids externally are seen to be swollen, thickened, hyperæmic, in some instances to such an extent as to suggest a mild attack of erysipelas. The tarsal conjunctiva and the fornix, usually both superior and inferior, are alike infected. Massive red hypertrophied papillæ, scattered over the tarsal conjunctiva, together with rounded button-like or flattened mushroom-shaped masses of granulation tissue, sometimes derived from the tarsal conjunctiva but usually springing from one or other fornix, characterise this form of conjunctivitis. (Many of these granulation masses, especially those springing from the fornices, are exceedingly irregular in outline, of a deep red colour, and bear a very close resemblance to the comb of the fowl; and it is a matter for some regret that the term "cockscomb excrescence" should have been used, by myself in common with others, in the description of appearances presented by Group IV., as the typical cockscomb excrescence is much more characteristic of Group III. than of Group IV.) On the tarsal conjunctiva between the hypertrophied papillæ may be seen areas that, beyond being of a livid purple-red hue, have not undergone any obvious naked-eye change. Here and there many of the masses of granulation tissue have undergone superficial necrosis, and thus present faceted ulcers covered with caseous material. Small circumscribed abscesses may be present. Here and there deposits of tubercles resembling those described in Group II. are to be seen, generally situated on the boundaries of the portions of comparatively normal conjunctival tissue. The bulbar conjunctiva almost invariably remains clear and unaffected, when remarkably little injection of the anterior conjunctival vessels is to be seen. The cornea in the early stages remains clear also, and this is the more astonishing in that owing to the œdema of the lids and the presence of the protuberant granulation a certain amount of ptosis is always present, so that the cornea is for the most part in contact with a highly infective granuloma. Cases comprised under Group III. have often in the past gone on for many years, and yet only in the very late stages have I noticed a slight amount of pannus, and even then no ulceration was to be made out.

Cases of this group may have to be distinguished from well-established trachoma, adenoma (lymphoma), simple granu-

lation tumour, angioma and malignant tumour, and very rarely can the diagnosis be made with certainty in the absence of bacteriological examination.

Group IV., Lupus.—Group IV. comprises those cases of tuberculosis of the conjunctiva which are simply extensions of true lupus from the adjacent areas of skin or mucous membrane. The appearances are those presented by lupus when it affects any mucous membrane, modified to a very slight extent by reason of the anatomical relations of the conjunctiva. In other words, the appearances presented are those of jelly-like masses, sometimes pale and greyish in colour, resembling nothing so much as frog's spawn, at other times deep crimson, and in no way differing from the red currant jelly masses found on skin surfaces. Occasionally the masses, particularly where they are springing from the fornix and are compressed between the lid and the globe, become flattened and sometimes pedunculated. Such excrescences, subjected as they are to intermittent pressure, usually exhibit more or less extensive ulceration, and acquire an irregular margin which explains the term "cockscomb excrescences" as applied to these structures to which I have already taken exception. Wherever ulceration occurs the ulcer is marked by a very steep, uneven margin, and bleeds very readily.

The diagnosis of cases falling in this group usually presents no difficulties whatever. The existence of lupus at the adjacent skin or mucous surfaces, and usually the clear evidence of the direct extension of the process on to the conjunctiva, renders no doubt possible. At the same time the possible co-existence with facial lupus of lesions other than tuberculous, such as those mentioned in connexion with the differential diagnosis under Group III., must not be lost sight of.

Group V., Pedunculated tumour.—This group comprises those cases which are characterised by pedunculated polypoid tumours, springing either from the conjunctiva of one or other lid or from the conjunctiva investing the globe. They are usually associated with no subjective symptoms other than those which arise from the extrusion of the mass from the palpebral cleft, and the certain amount of lacrymation which may result from the presence of a loose mass between the globe and the lids. The preauricular gland is not enlarged. Muco-purulent discharge is absent.

The clinical naked-eye examination absolutely fails to differentiate this form of tuberculosis of the conjunctiva from papilloma or fibroma, and one can safely say that the diagnosis can never be made with certainty in the absence of bacteriological investigation. True polypi, papillomata, and fibromata occur in the conjunctiva, as does also the granulation tumour, so frequently pedunculated, which sometimes accompanies the healing of various wounds or injuries or of ruptured chalazion, or forms around foreign bodies. On the

other hand, in none of the cases I have seen did the tuberculous tumour present any special character which would of itself raise any suspicion of tuberculous infection. In the first of these forms of tuberculous conjunctivitis that came under my notice search for the tubercle bacillus was undertaken simply on account of the recurrence of the tumour after excision. The detection of bacillus tuberculosis and consequent appreciation of the real etiological significance of this pedunculated tumour resulted in the systematic examination of all other similar tumours subsequently encountered, with the result that out of a total of 11 pedunculated conjunctival tumours the tubercle bacillus has been demonstrated in four.

(*b*) *Clinical Demonstration of Hypersensibility towards the Toxins of Bacillus Tuberculosis.*

In the individual suffering from tuberculous infection, whether localised or general, the phenomena of hypersensibility can readily be demonstrated by various clinical tests—known best by the names of their introducers or advocators. They all depend upon the introduction into that individual of the extracellular toxins of B. tuberculosis, either through the skin by various methods or through the uninjured normal conjunctiva.

For the first of these methods the original Old Tuberculin (Koch) is employed. This was first introduced in 1890 and is a clear brown aromatic-smelling fluid, prepared from a culture of B. tuberculosis grown for some 6 to 12 weeks in glycerin-veal broth, by evaporating it to one-tenth of its bulk and then filtering through porous porcelain. It is practically a glycerin solution of the extracellular toxins produced by the tubercle bacillus and for use is diluted with a 25 per cent. solution of glycerin.

For the last of these tests Old Tuberculin freed from Glycerin (Calmette) is utilised. This is prepared by treating Old Tuberculin with alcohol; the resulting precipitate is dried, dissolved in distilled water, again precipitated with alcohol, washed and dried. Before use it is dissolved in sterilised distilled water.

1. *Cutaneous reaction* (*von Pirquet*).—Three minute punctures are made through the epidermis, usually of the arm, in the form of a triangle with its apex upwards, by means of a small toothed lancet. The puncture at the apex is made directly on the skin. The other two, which mark the angles of the base of the triangle, are marked out each by a drop of 25 per cent. solution of old tuberculin and the puncture made through the drops. A positive reaction consists in the production at the end of 24 hours of a small hyperæmic area, which later becomes a definite papule, surrounded sometimes

by a distinct aureola of inflammatory reaction. The papule may or may not become pigmented.

2. *The dermal reaction* (Lignières, Lautier, Woodcock, or Moro).—Several modifications of this reaction are in vogue. Lignières and Lautier are in the habit of shaving off the epidermis from an area 1–2 square centimetres, so as to leave the dermis bare. Woodcock attains the same end by the use of a small blister plaster, 1 or 2 centimetres square. In either case a small quantity of 25 per cent. solution of old tuberculin is rubbed on to the denuded surface and allowed to dry. The inoculated spot is then covered with a small piece of protective gauze. A control area, not treated with tuberculin, is previously prepared at some little distance from the first. In Moro's modification old tuberculin is incorporated with an equal bulk of lanolin, and is thoroughly rubbed into the skin over an area of 1–2 cm., preferably with the aid of a small glass rubber or spreader. Whichever of these methods is employed, the positive reaction is shown after an interval of from 48 hours to three days by the appearance of œdema and hyperæmia over the area treated with tuberculin ; frequently a number of small papules make their appearance a little later, and may last for some days.

3. *The intradermal reaction* (Mantoux) is carried out by injecting into the substance of the skin itself about 0·05 c.c. (one drop) of a 1 in 5000 solution of glycerin-free (Calmette's) old tuberculin. Care must be taken that the injection is not made into the subcutaneous cellular tissue. A positive reaction is shown by the appearance within 24 hours of pink or bright red œdematous infiltration over the site of injection, with induration upon the surface, surrounded by a more or less extensive zone of erythema, very similar in appearance to an ordinary urticarial wheal.

Either of these tests applied to a patient suffering from tuberculous conjunctivitis would give rise to a positive reaction, but in interpreting the result two points must be borne in mind. The first is that a very large proportion of apparently healthy and normal individuals will yield positive reactions to these tests, thus supporting the view that a high percentage of the community at large is, or has been, the subject of tuberculous infection. I say *has been* advisedly, for the reason that many cases that gave cutaneous reactions during life when examined post mortem have showed no obvious tuberculous lesion or have given proof of past infection only (e.g., calcareous nodules in glands, &c.), but no evidence of present tuberculosis. So that I have come to regard a positive reaction to these tests when occurring in an individual more than one or two years old as quite useless for purposes of diagnosis. On the other hand, a negative result to any of these tests, especially if the same result is obtained on a repetition of the test a fortnight later, possesses, in my opinion, considerable value, as indicating that the tested

individual has hitherto escaped tuberculous infection. The second point is that none of the cutaneous tests can do more than indicate the presence of a tuberculous focus somewhere and in some tissue, they cannot determine the site of the lesion. A patient presenting extensive conjunctival ulceration might quite well give a positive reaction by reason of the existence of a tuberculous focus in a mesenteric gland.

4. *Subcutaneous test* (Koch).—In this test 0·001 c.c. of old tuberculin is injected hypodermically into any subcutaneous area. A positive reaction is indicated by the temperature commencing to rise some four or five hours after the injection, reaching a maximum in about 12 hours, and then gradually returning to its original level. A small localised indurated area at the site of inoculation may also be observed during the persistence of the pyrexia. This test obviously can only be employed in patients whose temperature variations are small, the existence, for example, of evening pyrexia being a strong contra-indication to its use. According to Koch, the rise of temperature following the inoculation to be of diagnostic value should not be less than a couple of degrees Fahrenheit. If, however, there is a slight rise of temperature—too slight to be of value as a diagnostic point—the inoculation should be repeated, employing the same dose, two days later. The second injection in the tuberculous individual will be followed by a pronounced rise, thus settling the point as to the positive reaction. If no temperature reaction, however slight, is observed the injection of a dose of tuberculin five times as large as the primary one, two days after that date, will give a distinct temperature reaction with a tuberculous individual, but will have no effect upon a normal individual.

The first objection I raised to the cutaneous tests may in some cases be urged in connexion with this subcutaneous test; but in the case of the individual suspected to be suffering from tuberculous conjunctivitis we have an obvious open lesion which can be critically observed, and the subcutaneous test, when positive, will, in addition to providing a temperature reaction, also produce very marked hyperæmia and tissue changes in the pre-existing tuberculous lesion; so that while the temperature reaction informs us that the individual is or has been tuberculous, the inflammatory reaction noted in the conjunctival lesion gives us the further information that that is the seat of the tuberculous focus. There is, however, a very valid objection to be raised to the employment of this test. The local reaction in the conjunctiva is by no means free from danger, but may be followed by a rapid and serious extension of the disease. Hence this test is also contra-indicated.

5. *Ophthalmo-test* (Calmette).—In this test, if one or two drops of a 1 per cent. solution of Calmette's glycerin-free old tuberculin be dropped into the normal conjunctival sac of a tuberculous individual, in the course of 24 hours a

distinct inflammatory reaction is observed in the conjunctiva, characterised by hyperæmia of the caruncle and plica semilunaris, injection of the conjunctival vessels, and lacrymation, which may increase in severity and give rise to the discharge of a muco-purulent secretion. This test, in my opinion, is the most valuable indication of the presence of an *active* tuberculous focus that we possess, so that it is a test I frequently employ to determine whether a tuberculous individual under treatment with tuberculin is or is not cured, discontinuing the injections only when a negative result is obtained. If both eyes are affected of course this test cannot be employed, as tuberculin should never be applied to an eye which is not to all appearance absolutely normal, nor, indeed, is it always suitable for employment in connexion with the diagnosis of lesions of the conjunctiva, since as with the subcutaneous test an inflammatory reaction may take place in the affected eye and give rise to serious trouble.

From the foregoing remarks it will be seen that of the various tests depending upon hypersensibility to tubercle toxin which may be employed for the diagnosis of localised tuberculosis in other situations of the body none are really suitable for our present particular purpose.

Results of Treatment.

We have in addition to the above methods of diagnosis one further clinical method to which reference may be made—I mean the results of treatment. If we assume that an individual presenting definite lesions is infected with B. tuberculosis, and treatment specifically directed towards the production of immunity towards the tubercle bacillus results in the disappearance of the lesion and the return of the individual to normal health, there is strong presumptive evidence that the lesion was due to infection with B. tuberculosis. In illustration of this point I may quote a case of scleritis recently transferred to me by one of my colleagues in which clinically the diagnosis between syphilitic and tuberculous infection remained in doubt. Wassermann's reaction gave a completely negative result. Von Pirquet's cutaneous reaction was positive. Calmette's ophthalmo-reaction applied to the sound eye was also positive. A series of opsonic indices indicated a tuberculous focus in the eye. It seemed justifiable therefore to assume that the case was one of tuberculous scleritis, and I presume that in earlier days the eye would have been excised, and in all probability the diagnosis completely settled, either by the detection of the tubercle bacilli in the infected tissues, or by the result of inoculation experiment. In this case tuberculin treatment was decided upon and resulted in the return of the eye to an absolutely normal condition in six months, thus confirming the original diagnosis.

Laboratory Methods.

(c) *Microscopical and Bacteriological Examination of the Local Lesions with a View to the Detection of Bacillus Tuberculosis.*

This method usually necessitates the excision of a portion or portions of the diseased conjunctiva under strictly aseptic precautions. In the case of Group I. excision is not absolutely essential from the point of view of diagnosis, since a gentle curetting will usually afford ample material for examination, but as excision is a recognised mode of treatment, the ulcer if small, should be entirely removed, together with any adjacent nodules. In some instances where the disease has progressed far, and the whole of the lid is infiltrated, a complete excision is well-nigh impossible, but even here a portion of diseased conjunctiva may well be removed, as undoubtedly the subsequent healing process will thereby be accelerated. The tissue removed should be received into a small sterilised glass capsule or sterilised test-tube containing a small quantity of normal saline solution warmed to 37° C., and at once conveyed to the laboratory and there divided into three portions.

1. One piece of tissue should be crushed in a sterilised glass or agate mortar, together with a small quantity of normal saline solution, and the resulting emulsion employed in the preparation of films. These should be stained by Ziehl-Neelsen's method and examined microscopically. Frequently the diagnosis can be confirmed by the detection of the tubercle bacillus within a very short time of removal of the tissue from the affected eye. If careful search of the film preparations fails to show the presence of tubercle bacilli, the remainder of the emulsion should be treated by the antiformin method. The emulsion should be added to a few cubic centimetres of antiformin [3] in a small test tube or capsule and placed in the hot incubator at 37° C. for about a couple of hours. At the end of this time the tissue will be found to be completely disintegrated, and the turbid fluid may now be centrifugalised thoroughly and the deposit used to make film preparations on albuminised slides, and stained by Ziehl-Neelsen's method. Frequently this plan will enable tubercle bacilli to be found where previously they were regarded as absent, and owing to the fact that antiformin used in this way destroys practically all bacteria except B. tuberculosis, this plan should be adopted if it is intended to attempt to cultivate the organism directly from the tissue—in which case the remainder of the deposit should be planted on to Dorset's egg medium in tubes.

[3] Equal parts of 16 per cent. solution NaOH and "Eau de Javelle."

2. The second portion of tissue should be hardened and embedded in paraffin preparatory to sectioning. The fixing reagent that is employed is a matter of little moment. Alcohol, perchloride of mercury, or formalin gives equally good results. I cannot, however, recommend the use of Müller's fluid. The sections should be cut as thin as possible and stained by Ziehl-Neelsen's method, and it will be found that aniline hydrochloride is a better decolourising reagent for sections than sulphuric or nitric acid. The preliminary staining with fuchsin and the subsequent decolourisation should be very carefully and thoroughly carried out, since in many cases the bacilli are not easily found. Other sections should be stained with hæmotoxylin and eosin in order to make out the general histological structure.

The results of the microscopical examination corresponding to each of the clinical groups may now be summarised.

Group I.—Microscopically scrapings from ulcers such as those already described show a considerable amount of caseous material mingled with numbers of small circular polynucleated granulation cells, and occasionally giant cells and epithelioid cells, amongst which may be found acid-fast bacilli, indistinguishable morphologically and tinctorially from the tubercle bacillus. These bacilli are often to be found in small bunches, and may be present in considerable numbers. Occasionally they are widely scattered throughout the films, and then occur either singly or in pairs. Microscopical examination of tissues in the immediate neighbourhood of the ulcers shows that, as in other forms of tuberculosis, the giant cell system is the fundamental basis of the tissue changes. Typical Langhans cells are to be found, although their numbers may be small, since the tissue contents comprise a very highly vascularised granuloma, rich in small round cells. Here and there masses with central caseation are to be observed, and it is at the periphery of these caseous areas that the tubercle bacilli are most readily found.

Group II.—Microscopically sections of the tubercles show very numerous and very well-defined giant cell systems, held together by connective tissue and surrounded by a minimal amount of small cell infiltration. Tubercle bacilli are scattered here and there, usually singly or in pairs, very rarely in bunches or groups, throughout the tissue, without holding any particular relationship to the central giant cells in the giant cell system. In numbers they are sparse, and very frequently a prolonged search is necessary in order to demonstrate their presence.

I have previously expressed the opinion that this group is but the initial stage of Group III. The small tubercles increasing in size by the proliferation of the small round-celled exudation which encircles the giant cell systems, in response to the irritating stimulus provided by the toxin of the tubercle bacillus, result in the fungating granulation so characteristic of Group III. or the papillary outgrowth of Group V.; alternatively, as I have also suggested, under circumstances indicating further differences in the relative activities of seed and soil, these tubercles may undergo necrotic degeneration and give rise to the miliary ulcers of Group I.

Group III.—Microscopical examination of sections of the tissue shows occasionally round and polygonal cells, but the bulk of the tissue is made up of small round cells held together by a scanty reticulum of connective tissue. Typical giant cell systems are conspicuous by their absence. Caseous areas are hardly ever seen, and tubercle bacilli, almost always single, are present in small numbers, and can only be found after very prolonged search. In two instances I have been able to detect tubercle bacilli in the muco-purulent discharge from cases of this group.

Group IV.—Microscopically the granulations consist of masses of small round cells like lupus elsewhere, which show in addition a large proportion of newly formed blood-vessels of the embryonic type. Here, again, tubercle bacilli are difficult to demonstrate. They are few in number, and so scattered through the granulation tissue that it requires considerable search before they can be found.

Group V.—Microscopically a layer of flattened epithelial cells usually only two or three cells thick, is seen enveloping the tumour. The tumour itself generally consists of a stroma of fairly dense connective tissue, enclosing a mass of round cells, with here and there giant cell systems, well defined, and typical in appearance. In close proximity to the giant cell systems tubercle bacilli can be found in fairly large numbers, arranged in bunches or occasionally as isolated individuals.

3. *Experimental inoculation.*—The third portion of tissue should be used for animal inoculation. The animals selected for the purpose are the rabbit and the guinea-pig, the seat of inoculation being the subcutaneous tissue of the groin in the case of the latter animal, and the anterior chamber of the eye in the former.

Of the two animals, the guinea-pig is generally considered to be the more susceptible to the tubercle bacillus, a successful infection resulting in death from general tuberculosis some six, eight, or ten weeks after inoculation. On the other hand, if tuberculous material be introduced into the anterior chamber of a rabbit's eye, an iritis which is almost pathognomonic follows in from 14 days to a month. The wide time limits given for the onset of iritis or the death of the guinea-pig from general tuberculosis depend upon two factors—the one, the virulence of the B. tuberculosis, the other the number of organisms introduced. In this connec, tion I may mention the experiments of Wyssokowitsch who (using tuberculous sputum) found that the fewer the organisms inoculated into the guinea-pig the longer the course of the disease before it was terminated by death, and also that if too few (less than 150) tubercle bacilli were inoculated into the rabbit tuberculosis was not set up. This point was also insisted upon by Koch in discussing the results which followed intra-ocular inoculation in the rabbit of varying quantities of culture material. Theobald Smith recorded a few definite experiments upon this point ; for example, an emulsion of a culture of the bovine bacillus was injected intravenously into a rabbit in a dose of 0·5 c.c. The remainder of the emulsion was diluted ten times, and another rabbit was inoculated with 0·5 c.c of this dilution. The first rabbit succumbed to general tuberculosis in 26 days ; the second did not die until 38 days after inoculation.

Now as the course and progress of a case of tuberculosis of the conjunctiva usually point to a strain of the tubercle bacillus of low virulence, and as one knows from microscopical examination of material from such cases that the bacilli are none too numerous, it follows that as large a piece as possible of the diseased conjunctiva should be used for inoculation purposes.

(*d*) *Biochemical Examination of the Patient's Blood Serum with a View to the Detection of Specific Antibodies.*

The examination of the patient by serological methods very frequently gives considerable assistance in diagnosis and treatment. The specific antibodies to bacillus tuberculosis which are generally the objects of search in these investigations are (1) agglutinins; (2) in general such specific antibodies as are capable of fixing complement; and (3) opsonins.

Agglutinins and complement fixing antibodies I do not propose to deal with in detail, as I do not consider either the sedimentation or the Bordet-Gengou reactions as applied to the bacillus tuberculosis sufficiently accurate or consistent to be of value in diagnosis—although both tests have their importance in regard to treatment. Opsonins, however, occupy a different position, and it will be well to present some of the special points in connexion with tuberculous conjunctivitis.

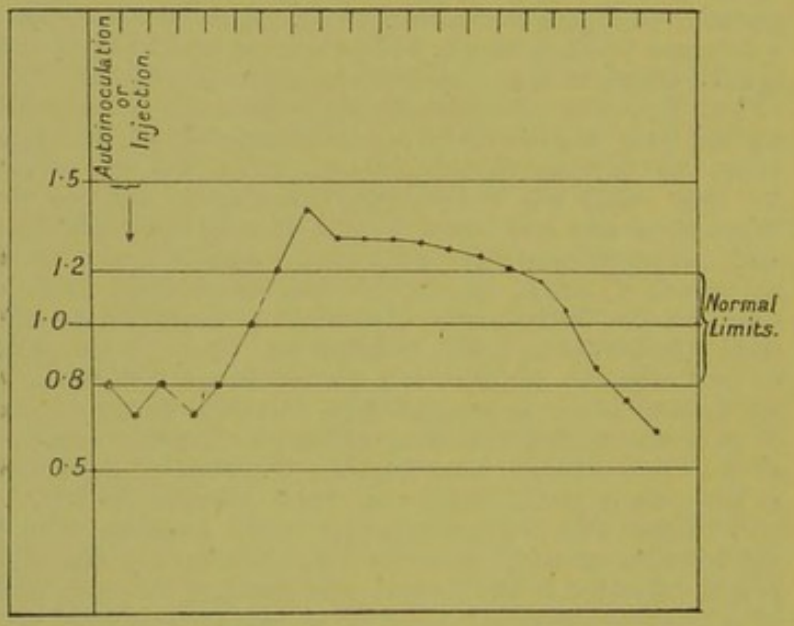
The diagnosis of tuberculous infection can be carried out by applying the method for the estimation of the opsonic index to (*a*) chance samples and (*b*) series of samples. To deal with the examination of chance samples first. Without in any way attempting to discuss the evidence for and against the intrinsic value of the opsonic index, it may be taken, I think, as fairly well established that the opsonic index in the hands of a skilled observer does afford some information as to the progress and course of the process of immunisation towards any given disease. Further, that the natural course of any infection is rather in the direction of cure, and during that progress certain definite movements of the opsonic index occur which are spoken of collectively as the opsonic cycle. Referring for a moment to Fig. 1, it will be seen that a chance sample might be taken from the patient at a moment when the index was at any one of the points indicated in the curve. The result of the examination of a chance sample of blood of a patient suspected to be suffering from tuberculosis of the conjunctiva may result then in an index to the tubercle bacillus which is either normal or considerably below or considerably above the normal line. In the first two instances the information obtained is of very little value. An exceedingly low index may mean either actual infection by the tubercle bacillus or merely susceptibility to infection by that organism. In the first case, the examination of another sample of blood may show movement of the index either to or above the normal, in which case we should be justified in assuming that infection had already taken place, but in the second instance another low index would still leave us in doubt, and further samples would be needed before a definite opinion could be arrived at. Similarly, in the case of the normal index further samples would be required in order to determine whether the index remained on the normal line, in which

case we should decide that the patient was not infected with the tubercle bacillus, or whether movements well above or below normal were obtained, in which case we should infer that infection had taken place.

An index considerably above the normal indicates with certainty the existence of a tuberculous focus (for Nature does not elaborate an excess of specific antibody, save in the attempt to overcome a definite infection).

It will, therefore, be seen that only under the most favourable circumstances can one hope to get definite and positive information as to whether the patient is or is not infected with bacillus tuberculosis from the examination of a chance sample, and that usually it is necessary to

FIG. 1.

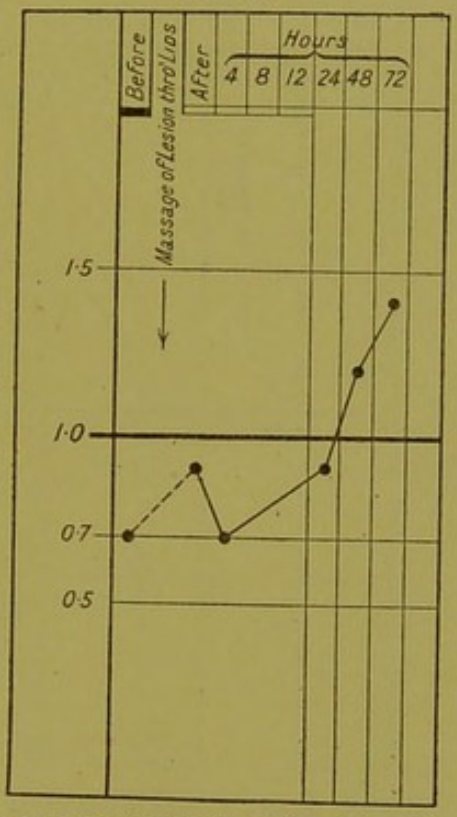


Opsonic index. Curve illustrating the question of *(a)* chance samples, or *(b)* series of samples.

examine two or more samples of blood. It is preferable, therefore, to arrange to examine a series of samples in the first instance, and this plan has a further advantage. Under ordinary circumstances neither the chance samples nor the series of samples give any indication as to the site of the lesion. They merely indicate the existence of a tuberculous focus, but if during the collection of the samples comprising our series we attempt to provoke an auto-inoculation, the information we shall obtain will not only tell us whether the patient is infected with bacillus tuberculosis, but if the question is answered in the affirmative will also tell us that the lesion from which we arranged the auto-inoculation should take place is the infective focus. In tuberculosis of

the conjunctiva it is no difficult matter to arrange that the auto-inoculation shall take place from the conjunctival lesions, since it is quite an easy matter to massage ulcers, tuberculous granulations, or polypi with the thumb or finger *through the closed lids* without causing any direct mechanical injury or producing any subjective sense of discomfort. The investigation should be carried out somewhat in this fashion. A sample of blood is taken from the lobe of the ear or from the patient's finger. Next the lids of the affected eye are kneaded between the two thumbs and moved over the globe for some three or four minutes. Half an hour later a second

FIG. 2.



Opsonic index in tuberculosis of conjunctiva. Curve showing effects of massage of eyelids.

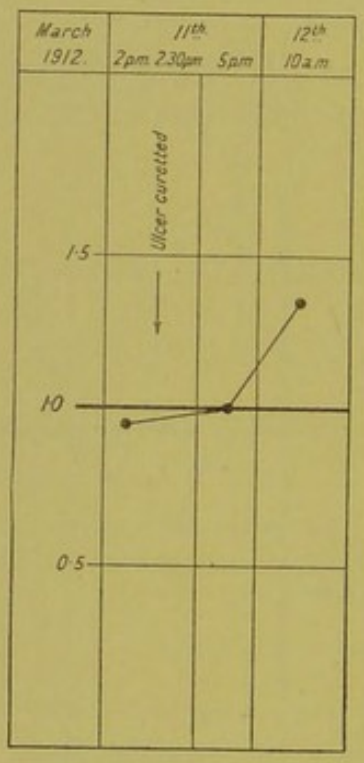
sample of blood is taken from the peripheral circulation. Three hours later, and 24 hours later, and perhaps three days later, further samples are taken. Should our clinical diagnosis be correct, and the patient be suffering from tuberculosis of the conjunctiva, a series of indices giving a curve somewhat resembling that shown in Fig. 2 will be obtained. Operative procedure upon the diseased conjunctiva will also provoke auto-inoculation, and specimens of blood taken before, soon after, and some 24 hours after curetting or the excision of a portion of the infected conjunctiva will usually give precisely similar information as in Fig. 3.

Etiology.

A. *Predisposing Causes.*

In many infective diseases a careful consideration of the causes which may possibly influence infection, such, for example, as sex, age, &c., will afford valuable information, but in the case of tuberculosis of the conjunctiva the only feature which stands out with any degree of prominence is that the disease affects individuals chiefly during the early years of life. In this respect, however, it differs in no wise

Fig. 3.



Opsonic index. Effects of curetting conjunctival ulcer.

from tuberculosis in other situations. Whilst investigating these predisposing causes the literature has been carefully searched for details of recorded cases, and in order to be consistent no case has been included in which the diagnosis was lacking in the essential point—namely, the demonstration of the presence of bacillus tuberculosis. This means, of course, that no cases prior to the discovery of the tubercle bacillus in 1882 have been included, but even in those recorded since that date it is a striking fact that precise details are lacking in a considerable number. In all I have analysed nearly 400 recorded cases, and from these I have been able to select less than 200. Unfortunately, in some

TABLE I — *Giving Details of 29 Cases of Tuberculosis of the Conjunctiva.*

Group.	No.	Sex.	Age.	Tuberculosis history, family or personal.	Eye affected.	Situation of lesion.	Glands involved.	Tubercle bacillus in lesion.	Inoculation experiment.	Treatment.	Result.
I.	1*	M.	5/12	—	Right.	Palpebra inferior.	Preauricular.	+	+	Operation.	Cured.
	2*	M.	7½	—	,,	Bulbar.	,,	+	0	,,	,,
	3	F.	3 6/12	—	,,	Palpebra superior.	,,	+	+	T.R. 14 months.	Cured. Tuberculous skin lesion later.
	4	M	6	—	,,	Palpebra superior + inferior + bulbar.	Preauricular + sub-maxillary.	+	+	T.R. 2 months.	Improving rapidly.
II.	5*	M.	20	—	,,	Palpebra inferior.	Preauricular.	+	0	Operation.	Cured.
	6*	M.	1 5/12	—	,,	Palpebra superior.	,,	+	0	,,	,,
	7	M.	5	—	,,	,,	,,	+	+	,,	,,
	8	F.	1 6/12	—	,,	Palpebra superior + inferior.	,,	+	+	T.R. 12 months.	,,
	9	F.	7	Family.	,,	Palpebra superior.	,,	+	+	Operation.	,,
	10	F.	27	—	Left.	Bulbar.	,,		+	T.R.	?
	11	F.	20	Family.	,,	,,	,,	−	+	T.R. 4 months.	Cured.
III.	12*	F.	23	Personal.	Both.	Palpebra superior + inferior.	,,	+	+	Operation.	No improvement.
	13*	F.	23	,,	Right.	Palpebra inferior.	,,	0	+	,,	Improved.
	14†	M.	18	—	,,	Palpebra superior + inferior.	Preauricular + sub-maxillary.	+	+	,,	Cured.
	15†	M.	14	—	Left	,,	Preauricular.	+	+	,,	Improved.
	16‡	F.	9	Family.	,,	Palpebra superior.	,,	+	+	T R. 12 months.	Cured.
	17	M.	13	—	,,	Palpebra superior + inferior.	Preauricular + sub-maxillary.	+	0	T.R. 13 months.	,,
	18	F.	15	—	Right.	Palpebra superior.	Preauricular.	+	+	Operation.	,,
	19	F.	19	—	Left.	Palpebra superior + inferior.	,,	+	+	,,	No improvement.
	20	M.	15	—	Right.	,,	,,	+	+	T.R. 6 months.	Cured.
	21	M.	12	—	Left.	,,	,,	0	+	,,	,,
	22	M.	14	—	,,	,,	,,	+	+	Operation.	Recurred. Died 2 years later from general miliary tuberculosis.
IV.	23*	M.	15	Personal.	,,	Palpebra inferior.	,,	+	0	,,	Recurred.
	24	M.	49	,,	,,	Bulbar.	*Nil.*		0	T.R. 4 months.	Much improved.
	25	F.	14	,,	Right.	Palpebra superior + inferior + bulbar.	Preauricular.	+	0	T.R. 7 months. Operation.	No improvement. Improved.
V.	26*	F.	28	—	,,	Palpebra inferior.	,,		+	Operation.	Cured.
	27*	F.	9	Family.	Left.	,,	,,	+	0	,,	No local recurrence, but right apical phthisis twelve months later.
	28	F.	5 6/12	—	Right.	Palpebra superior.	,,	−	+	,,	Cured.
	29	F.	8	—	,,	Palpebra inferior.	*Nil.*	−	+	,,	,,

* Recorded 1897. † Recorded 1900. ‡ Recorded 1908.

of these, although the report is full and accurate in many respects, such details as the age or sex of the infected individual, and even the eye affected, have been omitted. To these cases I have added those which have come under my own observation, and which now number 29 (omitting one recent case in which the diagnosis was not substantiated by the demonstration of the specific bacillus, as this could only have been done by sacrificing the eye—which under treatment with tuberculin has been saved and retains normal vision). By doing this a total of 206 authentic cases has been rendered available for analysis. The chief points in the histories of my own cases are here summarised in tabular form (Table I.), and I take the opportunity of expressing my thanks to my colleagues at Guy's, Dr. H. L. Eason and Mr. A. W. Ormond, for the cases they have sent on to me.

Sex.—From the analysis of these cases (Table II.) it would appear that sex has but little influence upon the etiology of tuberculous conjunctivitis. Females, however, preponderate, since there are 112 females and 88 males; in the remaining six instances either the sex or age of the patient—or both—is missing from the author's account of the case; so that if these six cases are disregarded we find 44 per cent. of the patients were males and 56 per cent. females. In 1897 I expressed the opinion that the ratio was about 1·5 females : 1 male, but the present investigation shows a ratio of only 1·27 : 1, and I take it merely expresses the fact that there are slightly more female conjunctivæ available for infection during the age period of greatest incidence.

TABLE II.—*Analysis of 206 Authentic Cases, showing Age, Sex, and Clinical Grouping.*

Age.	Group I.		Group II.		Group III.		Group IV.		Group V.		Totals.	
	M.	F.	M	F.	M.	F.	M.	F.	M.	F.	M.	F.
0–10 years	11	11	5	6	8	11	1	—	1	3	26	31
11–20 ,, ...	2	10	4	4	17	16	9	16	1	2	33	48
21–30 ,, ...	1	3	1	3	5	7	3	7	—	1	10	21
31–40 ,, ...	3	1	1	—	3	3	—	3	—	—	7	7
41–50 ,, ...	1	1	—	—	—	1	3	1	—	—	4	3
51–60 ,, ...	0	1	—	—	2	—	1	—	—	—	3	1
61–80 ,, ...	1	0	—	—	4	—	—	1	—	—	5	1
Age or sex (or both) unspecified ...	(0)		(1)		(3)		(1)		(1)		(6)	
Totals	19	27	11	13	39	8	17	28	2	6	88	112*

* 200 + (6).

Age.—The age limits within which cases of tuberculosis of the conjunctiva occur are extremely wide. No less than four patients in this series were under 12 months—namely, one recorded here by myself at six months, one by Del Monte at eight months, others by Ulrich and myself at 10 months. At the other extreme are cases by Terson, 71, and Hochheim, 76 years. Still, just as in other localised forms of tuberculosis, its onset is usually during childhood and early adult life, 57 cases occurring during the first ten-year period and 81 during the second, and is most marked at or about puberty.

Eye affected.—In this series of 206 cases the eye which was the seat of the lesion is not recorded in 24 instances; of the remaining 182 the right eye was the affected one in 44·5 per cent. and the left in 43·4 per cent., so that neither eye can be said to be more frequently attacked than its fellow, since the figures are practically equal. It is exceedingly uncommon for both eyes to be affected; only 22 such cases have been recorded, or 12·1 per cent. of the series, as against 87·9 per cent. where one eye only suffered.

Right eye	81
Left eye	79
Both eyes	22
Not specified...	24
	206

Situation of the lesion.—In 7 cases the seat of the lesion is not specified. The situation of the lesion in the remainder is as follows:—

Conjunctiva of upper lid...	62
,, lower lid	30
,, both lids...	59
Bulbar conjunctiva	31
,, ,, and both lids	12
,, ,, ,, lower lid	4
,, ,, ,, upper lid	1
Not specified	7
	206

It would therefore appear that the conjunctiva of the upper lid—the favourite spot for the lodgment of a foreign body be it noted—was that most frequently selected for attack by the bacillus tuberculosis. Next in order of frequency both lids were involved when the patient first came under observation, and it is only fair, I think, to assume that one lid was infected at a date prior to the other, and probably the ratio of about 2 : 1 in favour of the upper lid would hold good in these, so that *quâ* site of

primary lesion the series would probably be better grouped thus :—

Upper lid	62
Lower lid	30
Bulb	31
Combinations of above, in which the original site of infection cannot be assumed	83
	206

Family medical history.—A history of tuberculous disease in the parents or grand-parents may fairly be reckoned as a factor in the etiology of tuberculosis of the conjunctiva for two reasons. In the first place, it is a matter of common experience that the offspring of tuberculous individuals exhibit a certain susceptibility towards bacillus tuberculosis —and indeed to many bacteria—probably on account of low cell resistance; and secondly, association with tuberculous individuals in the intimacy of family life affords so many opportunities for infection that are avoided by members of healthy families. But when dealing with tuberculosis of the conjunctiva other than lupus one is struck by the absence of tuberculous family histories, and in some of the reports stress is laid upon the fact that no history of tubercle, family or personal, could be obtained. In four of my own cases there was a history of a phthisical relative or fellow worker.

Personal medical history.—Again, considering the number of cases in which multiple tuberculous lesions are present, a personal history of tuberculosis is of importance, but (once more excluding the cases of lupus) out of the remaining 160 cases of tuberculosis of the conjunctiva there are only 7 in whom pulmonary tuberculosis existed at the time they came under observation. In two others tuberculous cervical glands associated with lupus had existed prior to the conjunctival lesion, which from the clinical point of view was itself not lupus of the conjunctiva (Group IV.), but belonged to Group III. These facts are in striking contrast to the findings in intra-ocular tuberculosis, where, as Treacher Collins[4] has pointed out, tuberculous family and personal histories are the rule rather than the exception.

B. *Exciting Cause.*

The exciting cause, the real etiological factor in tuberculosis of the conjunctiva, is the tubercle bacillus. Considerable importance is being attached at the present time to the differentiation of the tubercle bacillus, isolated from lesions in man, into one of two main types, the human and the bovine. In 1898 Theobald Smith drew attention to the existence of two varieties of the tubercle bacillus, the one

[4] Intra-ocular Tuberculosis, Ophthalmoscope, No. 5, 1907, p. 11.

which he had isolated from human sputum, and the other from tuberculous lesions in cattle, and pointed out certain material distinctions which could be drawn between the two types ; but although his investigations attracted some notice it was still considered that these differences, probably due to environmental influences, were of but minor importance, and that all mammalian tuberculosis was due to the same micro-organism. At the Tuberculosis Congress in 1901, however, Koch expressed the opinion that human and bovine tuberculosis were two separate and distinct diseases, and due to two separate and distinct acid-fast bacilli. It will be fresh within your memory that a Royal Commission was appointed to investigate the subject, and its report, recently published, confirms in effect Theobald Smith's observations—namely, that there are two types of tubercle bacilli, the human and the bovine, of which the bovine is not only the exciting cause in bovine and animal tuberculosis, but is also responsible for some 20 per cent. of the tuberculous infections in man. It is, therefore, a matter of some importance to determine whether tuberculosis of the conjunctiva as a whole, or in one or more of the five generally accepted types, is due to infection with the bovine tubercle bacillus. Before, however, dealing with this question it will be well to summarise the data upon which a distinction between human and bovine tubercle bacilli can be based. The tubercle bacillus of the bovine type is quite short, from 1–1·5μ, straight, not regular in outline, some individuals being wedge-shaped, some spindle-shaped ; others resemble oval cocci It grows with difficulty upon artificial media, and is highly virulent for the ordinary laboratory animals, particularly the guinea-pig and the rabbit. Thus, in the adult guinea-pig subcutaneous inoculation of bovine tubercle bacilli (artificial cultivations) results in the occurrence of extensive lesions, marked by necrosis and caseation and the presence of numerous bacilli, death ensuing in from 4 to 6 weeks. Intraperitoneal inoculations produce similar effects and cause death in from 7 to 14 or 15 days. Intravenous inoculations into the rabbit produce death in 17 to 21 days. Inoculations into the anterior chamber of the eye give rise to iritis in 7 or 8 days and produce death in 3 weeks.

The human tubercle bacillus is long (about 3μ) and slender, straight or slightly curved, and very frequently shows segmentation of the protoplasm, so that the stained bacillus closely resembles a short chain of cocci. It grows readily and vigorously upon artificial media, and although virulent for the guinea-pig and rabbit, is markedly less so than the bovine bacillus. Subcutaneous inoculation into the guinea-pig results in the formation of slight lesions, the tubercles growing but very slowly and long remaining translucent, with a tendency to reparative changes. The course of the infection is chronic, necrosis is rare, bacilli are very scarce, and death does not usually occur under 12 weeks.

Intraperitoneal injections more rapidly produce a fatal termination, the course of the infection being from four to six weeks. Intravenous inoculations into the rabbit give rise to an infection which terminates fatally in five weeks or longer, while inoculations into the anterior chamber of the eye give rise to iritis which develops in about four to six weeks.

In the recorded cases of tuberculous conjunctivitis on mention is made of any investigation into the question of the type of bacillus tuberculosis present in the lesions. But although no information has hitherto been communicated with reference to this differentiation, some of the material from my own cases, even the early ones, is still available, and it is interesting to note that this re-study of my sections has shown the presence of tubercle bacilli in tissues from cases where I had previously relied solely on the result of inoculation experiments for the confirmation of the diagnosis. It must, however, be recollected that I am presenting my results rather in the form of a pious opinion than of incontrovertible fact, since, as I have been unable to carry out cultural experiments, the tubercle bacillus has not been isolated and fully studied. I have therefore been forced to depend upon the morphology of the bacilli present in the sections of tissue, and upon the results of the inoculation experiments, applying the following criteria. Where the bacillus first observed has been long, slender, moniliform, and has not caused the death of the inoculated guinea-pig until after some time, I have regarded this bacillus as belonging to the *typus humanus*. When, on the other hand, the bacillus in the tissues has been short, irregular and evenly stained, and has produced rapidly a fatal general tuberculosis in the inoculated guinea-pig, I have regarded this organism as belonging to the *typus bovinus*. The fallacies are obvious. In the first place, as the Tuberculosis Commission has pointed out, numerous intermediate types of the tubercle bacillus exist with morphological characters midway between the extremes I have described, and in the second the course of a tuberculous infection is very largely a function of the size of dose—in other words, the numbers of bacilli introduced—as I have already mentioned, and variations in this respect produce corresponding variations in the duration of the disease, in its final termination, and in the extent and distribution of the lesions.

With a full appreciation of these points I place my results before you in tabular form, from which it will be seen that the human tubercle bacillus is assumed to be responsible for at least 62 per cent. of my cases and the bovine strain for about 17·2 per cent. No material was available for examination from the lupus case, but as lupus in general is considered to be due to infection by the human type, it is almost justifiable to regard this strain as the exciting cause in 72·4 per cent. But to avoid anything approaching dogmatism I will say that I regard the human type of tubercle bacillus as that usually

responsible for the infection in tuberculous conjunctivitis, particularly in those cases where the lesion affects the type seen in the third clinical group, and the bovine type as an unusual exciting factor.

TABLE III.—*Showing the Type of Tubercle Bacillus present in Tuberculosis of the Conjunctiva.*

Clinical group.	Number of cases.	Bacillus tuberculosis.		Material lacking or result of examination doubtful.
		Human type.	Bovine type.	
I.	4	2	1	1
II.	7	3	2	2
III.	11	11	0	0
IV.	3	0	0	3
V.	4	2	2	0
Totals...	29	18	5	6

PATHS OF INFECTION.

Infection of the conjunctiva by the tubercle bacillus may be derived either from exogenous or endogenous sources.

Exogenous Sources.

1. *Direct extension by continuity of surface from pre-existing tuberculous lesions.*—This is the path of infection in cases of lupus of the conjunctiva, the spread taking place by continuity of surface either through the lacrymal duct from the mucous membrane of the nose, or from the adjacent skin surface of the face. Primary lupus of the conjunctiva I have never seen, and in the one or two recorded cases the evidence has not been sufficiently convincing that this direct extension had not taken place. Further comment on this path of infection is unnecessary.

2. *Direct inoculation of the conjunctiva.*—In 1897 I stated that "the conjunctival lesion is nothing more than a direct local infection resulting from the introduction of tuberculous material into the conjunctival tissues, and it may be safely assumed that in the cases belonging to Groups I., II., and V. this is invariably the case." That this opinion is correct in the majority of instances I am still prepared to maintain, and I will now summarise the points in its favour.

(*a*) In the vast majority of these cases there is a total absence of evidence of the existence of tuberculous lesions elswhere in the body.

(*b*) Frequently strong evidence is obtainable of exposure of the patient to tuberculous infection in the persons of relatives, friends, or companions in work or play, or at school. In this connexion may be mentioned Birch-Hirschfeld's case of the cowman who was in the habit of milking a cow with tuberculous disease of the udder, and who subsequently developed tuberculosis of the conjunctiva of the second group.

(*c*) Many instances of the very act of inoculation can be adduced, as, for example, Fano's case and also Knapp's, following tenotomy, and Pregel's, in which infection was conveyed by a foreign body.

(*d*) Experimental evidence shows that the inoculation of tuberculous material upon the conjunctival surface of the lid of the rabbit will result in the formation of definite tubercles resembling those met with in the second group, and in one instance at least I have seen these tubercles caseate, necrose, and break down into ulcers similar to those observed in the human subject in the first group.

(*e*) Anatomically the primary lesion—the miliary tubercle—usually makes its appearance, if bulbar, at or near the corneal margin on the equatorial line; if palpebral, on the tarsal conjunctiva, somewhere midway between the lid margin and the fornix, sometimes in the interval between adjacent Meibomian glands. Where several tubercles are present on the tarsal conjunctiva they take a linear arrangement, roughly parallel to the lid margin. The dense connective tissue forming the tarsus appears to offer a complete barrier to the extension of the infective process in this direction, and extension takes place only through the conjunctiva itself in the direction of the lymph-flow—that is, towards the fornix—where the laxity of the tissues and the volume of the blood-supply combine to favour rapid cell proliferation and the formation of exuberant granulations.

(*f*) Histologically the infective process can usually be shown to originate in the adenoid tissue of the substantia propria of the conjunctiva or in or around the glands of Henle. Occasionally the infection appears to have originated in or in close proximity to the lateral diverticula of the Meibomian glands. In any case, the infective process is marked by cell proliferation and exudation to such an extent that the conjunctiva superficial to the tarsal cartilage becomes enormously hypertrophied, often to 40 or 50 times its normal thickness.

So that my previous opinion as to the pathology of tuberculosis of the conjunctiva of the first, second, and fifth types remains unaltered; that is to say, it is practically always the result of the direct inoculation of tubercle bacilli, possibly (1) between the interstices of the epithelial cells of an apparently normal conjunctiva (since we know that such infection can readily take place in the case of another organism, micrococcus melitensis); (2) into a broken-down phlyctenule; (3) into an occluded or possibly a ruptured Meibomian gland; and (4) into some abrasion or other slight trauma. I do not deny, however, the possibility of an endogenous source of infection in these cases, and to this point I shall refer in a moment.

The infective virus can be obtained from many sources: (1) From contact with phthisical relatives, friends, playmates; (2) by conveyance from similar sources by soiled handkerchiefs, towels, and so on; (3) by dried particles of infective material floating in currents of air (for it will be seen that I assume the majority of infections are due to inoculation with the human type of tubercle bacillus); and (4) possibly by the transference of infective milk by fingers or otherwise to the conjunctival sac.

Endogenous (Hæmic) Sources.

That tuberculous conjunctivitis may occur as part of a general tuberculous infection is shown by an experiment noted by Theobald Smith, where a rabbit inoculated intravenously with a culture of tubercle bacillus developed three flattened disc-like excrescences—lesions of the conjunctiva corresponding to Group III. as it occurs in the human subject; he also states that nodular thickening existed in both lids *external to the lobules of the Meibomian glands*. One human case, which I have already referred to, where tubercles corresponding to those of Group II. appeared on the bulbar conjunctiva immediately over an area of scleritis already diagnosed as tuberculous, affords support to the possibility of this method of infection. This, however, is an isolated case.

Theobald Smith's example of an infection of the conjunctiva from the blood stream was the only instance observed throughout the course of his experiments. I have tried to repeat it, but without success, even when an attempt has been made to determine localisation of the bacilli to the conjunctiva by trauma.

Moreover, during the course of the last 15 years I must have inoculated tuberculous material by various channels into hundreds of rabbits and guinea-pigs for purposes of diagnosis, and have produced generalised tuberculosis in considerably more than half of these experimental animals, but in no single instance have I produced conjunctival lesions except in those cases where the conjunctiva has been the seat of the inoculation.

Also from a consideration of the blood-supply of the eye and its appendages it would appear most probable that in a hæmic infection of the intensity that would occur naturally the bacilli would be carried by the central artery to the interior of the globe, and would most probably settle in the plexuses of the free or attached margins of the iris—and this is what usually happens in experimental hæmic infections—or if taken on by the lacrymal and palpebral arteries would be more likely to settle in the superficial structures of the eyelid in some portion of the tarsal arch—that is, external to the lobules of the Meibomian glands, a condition I have not yet seen—rather than proceed onwards with the minute vessels that pierce the tarsal cartilage to infect the conjunctiva beyond.

For these various reasons I cannot but regard this method of infection, although possible, as extremely rare.

Treatment.

Although I am at the moment hardly concerned with the question of treatment, I cannot refrain from adding some remarks upon the subject. One spontaneous cure has been

recorded, and although it is unlikely that many tuberculous lesions of the conjunctiva undergo such complete retrogressive and reparative changes, the first measures should undoubtedly be directed to increasing the resisting powers of the tissue cells of the infected individual by attention to general hygiene, abundance of fresh air, generous diet, regulation of the body functions, and the exhibition of any constitutional treatment—e.g., malt, cod-liver oil, iron, arsenic, &c.—that may be indicated.

The assistance of X rays has been invoked by several observers, and eminently successful results have been recorded by Cassali, Stephenson, and others. Fifteen years ago, when discussing this subject, I wrote that "the treatment of tuberculosis of the conjunctiva must be conducted upon lines precisely similar to those which guide us in the treatment of local tuberculous lesions in other organs —viz., early and complete removal of the diseased area. The means by which this end is attained, whether by the use of the knife, the sharp spoon, or the galvano-cautery, must be left to the discretion of the individual surgeon, but it is obvious that the removal of the affected tissues must be thorough. If any of the tuberculous material whatever be left *in situ* it may, and possibly will, become the starting-point of a general tuberculosis."

In one of my own cases this apparently happened. The conjunctival lesion was removed from a child in whom no other tuberculous lesion could be demonstrated. When seen 12 months later there was no local recurrence, but the lungs were undoubtedly infected. Another case developed general miliary tuberculosis six months after excision of the diseased conjunctiva and died. In a third a patch of lupus made its appearance on the thigh. In the recorded cases I have analysed two subsequently developed pulmonary tuberculosis, and two others tuberculous pleurisy.

Again, "in advanced cases, where large areas of tissue are involved, complete removal is not always practicable, and a permanent cure must not be expected. Under these circumstances palliative treatment only can be pursued."

Since then my views have undergone some modification. I still advocate the complete removal of the local lesion if that can be done without risk of subsequent scarring and disfigurement, or of injury to the globe, in cases coming under Groups II. and V. Also in Groups I. and III. any scraping and cutting that will remove any considerable portion of the diseased tissue without involving similar risks should certainly be carried out, but in addition I strongly advocate the administration of Koch's tuberculin T.R. Carefully administered by the skilled observer the conjunctival lesions become absorbed—indeed, they may almost be said to melt away—and the conjunctiva returns to its original normal condition. Scarring and deformity are avoided. The infected glands, preauricular and submaxillary, also undergo resolution in most instances, although sometimes, if casea-

tion has taken place before the case comes under observation, they will need opening and clearing out. In his Middlemore prize essay Bryan records one case of his own which resulted in a cure after 45 months' treatment, refers to Saxl's case (which was treated intermittently for three months and recorded as unsuccessful) and to the one shown by Mr. A. W. Ormond and myself to the Ophthalmological Society as cured after 12 months' treatment, and sums up by saying: "The results, then, of treatment of tuberculosis of the conjunctiva are good provided the treatment be persisted in over a long period." With his conclusion I agree. Since my first case in 1907 (admitted to Guy's Hospital under the care of Mr. Ormond) I have employed tuberculin in 10 others, making 11 in all. Of these 11 cases one, lupus of the conjunctiva extending from the face (treated with excision and tuberculin for four months), was much improved, and has not relapsed in the 12 months that have elapsed since he took his discharge, and one has only just commenced treatment. A third, lupus of the conjunctiva extending in this instance from the nasal mucous membrane, was not benefited in the least. Bovine tuberculin, human tuberculin, X rays, and radium were all tried in vain. Finally, a certain amount of relief has been afforded by operative measures, in the course of which practically the whole of the nasal septum was removed, as well as the conjunctival lesion. The remaining eight cases have been completely cured after treatment extending over periods varying from 4 to 14 months. The tuberculin used has been Koch T.R. (human) in 10 of the cases. My initial dose has been as small as 1/20,000 mgr. and my maximum dose has never exceeded 1/2000 mgr. The intervals between the doses have varied from seven days to three weeks.