pany "gastric hurry" as indicated by x-rays or the fractional test meal. The same feelings occur in the presence of a duodenal ulcer, and may replace as well as accompany the more characteristic "hunger-pain." "Pressure" and "wind" two or three hours after food are other variants on the epigastric "gnawing" of duodenal ulcer, and I have known the diagnosis to be missed in many cases because the patient insisted on the use of these words in preference to "pain."

Nausea we have all experienced, and while it may be felt as high as the pharynx it is also commonly an epigastric sensation. Experienced in the early morning, before food is taken, it is a familiar symptom of pregnancy and gastritis, whether alcoholic or infective. In association with headache it is a symptom of migraine or occasionally of astigmatism; with tinnitus and vertigo of labyrinthine disease. Coming at irregular intervals and "in waves" it is a common symptom of biliary tract infection. When transitory, and especially in young women, and when felt in the throat, it may express emotional disturbance.

Of the physiology of all these symptoms we still require more accurate knowledge. Experimental studies, radiology, and clinical inference from associated objective findings have, however, given us reason to suppose that "heartburn" is due to minor spasmodic contractions of the gullet; that nausea is due to relaxation or a sub-normal tonus in the gastric or pharyngo-oesophageal musculature; that "pressure feelings" often accompany exaggerated tonic action; that "sinking" accompanies the increased peristaltic and tonic activity of emptiness and hunger; that a normal air-content in a hypertonic stomach or excess of air in any stomach as the result of aerophagy may give rise to sensations of "pressure"; and that neither a high nor a low nor an absent acidity is capable of giving rise to any distinct sensation in the epigastrium whatsoever, although acid eructated into the pharynx produces a scalding sensation there.

Gastric Flatulence

Gastric flatulence may be odourless or foul. When it is foul it is generally due to putrefaction of food in a stagnant viscus and is usually symptomatic of pyloric stenosis or obstruction. It has the odour or flavour of sulphuretted hydrogen. It is not produced in sufficient quantities to cause gastric discomfort by itself or to occasion frequent or noisy belching. Eructation of bowel flatus is diagnostic of a gastro-colic fistula, which may complicate an anastomotic ulcer or a carcinoma of the transverse colon.

The amount of gas produced in the stomach by diffusion is probably too small to cause symptoms of any kind. Odourless gas which leads to frequent or noisy eructation may, in fact, be partly or wholly attributed to aerophagy in every case. It should, however, be remembered that aerophagy can occur in the presence or absence of an organic disease. The act of eructation is noticeably preceded by a gulp with closed lips. In nervous subjects aerophagy may be the whole cause of a persistent dyspepsia of many years' duration. In such cases it may sometimes be cured by a simple explanation at a single sitting.

Of the organic states complicated by aerophagy gallstones and duodenal ulcer are, perhaps, the commonest. I am inclined to think that aerophagy also helps to explain the eructation which concludes and seems to relieve some anginal attacks. This association with angina and the arrival of anginal pain after meals account for many mistaken diagnoses. I have not been at pains to discover how many cases of angina have been referred to me as dyspepsias, but I know it is no inconsiderable proportion of the whole.

Conclusion

It has been my chief purpose to indicate the important part which a close analysis of common symptoms may play. It would take too long to buttress my belief in such analyses by case-histories for the simple reason that in the more difficult cases it is only by very detailed analyses that results are achieved. In straightforward cases a brief and simple interrogation is often adequate. In difficult cases time spent in a long interrogation is never wasted time. To-day we have the radiologist and chemist to help us, but they cannot diagnose coronary artery disease or early carcinoma of the liver, and in the great majority of cases of epigastric discomfort and flatulence they would be compelled to report negative findings. Negative findings may be very valuable, but of equivalent or greater value is a positive conclusion based upon a knowledge of the patient's body, and mind, and environment, and a reasoned physiological interpretation of his subjective complaints.

THE TUBERCLE BACILLUS AS A CAUSE OF OBSCURE DISEASE OF THE EYE*

BY

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This subject is of great importance, and although it is not yet possible to arrive at any definite conclusions the time has come for us to review the available evidence, even if the result of our doing so is to return that useful Scottish verdict of "not proven."

Friedenwald,¹ in a book published in 1930, says that "an uninitiated reader of the literature might easily be led to suppose that in Germany and elsewhere on the Continent tuberculosis is quite a different sort of disease from that which we find in this country, while, on the other hand, the teeth and tonsils of the British and American people were in some obscure way stimulated to most malicious behaviour." Such a statement is, I think, largely true to-day, though the supposed ravages of the tubercle bacillus are possibly covering a wider area in the Anglo-Saxon countries than was the case six years ago.

One of the functions of the opener of a discussion is to attempt to define its limits, and here I am in a quandary through the use of that indefinable adjective "obscure." Used in its present context I take it to exclude all obviously tuberculous lesions such as conglomerate tubercle of the iris, miliary tubercles of the choroid in the terminal stages of tuberculous meningitis, and so on. What diseases, then, ought we to consider, or, to put it another way, what diseases of the eye, although at first sight they are not obviously tuberculous, can be ascribed to the activities of the tubercle bacillus?

In the conjunctiva the outstanding example is phlyctenular disease. Mr. Sorsby has done some excellent work on this subject, and I hope he will speak on his findings. In the cornea there are various types of deep keratitis and possibly some of superficial punctate keratitis. The uvea is, of course, a "gold mine" for the tubercle enthusiast, and according to some of the Continental observers almost every type of iritis, iridocyclitis, and choroiditis may have a tuberculous origin, including sympathetic ophthalmitis. In the retina, apart from contact infection from the choroid, perivasculitis, retinal haemorrhages, retinitis proliferans, and angioid streaks are on the list, while in the optic nerve there are retro-

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bulbar neuritis and thrombosis of the central vein, especially in the young. In the sclera any inflammation, especially the superficial variety, may have a tuberculous basis. This is a fairly comprehensive list, and I do not propose to weary you by going through it seriatim; in fact, I would rather pass on now to a general consideration of the evidence on which a tuberculous aetiology can be suggested.

Infection of the Eye by Tubercle Bacillus

In the first place, Finnoff's papers² are of fundamental importance. They constitute an amplification of the work of previous observers such as Friedrich and Nösske³ and Stock.⁴ In his earlier paper Finnoff tells how he injected clumps of living tubercle bacilli into the carotid arteries of rabbits and produced lesions in the eyes of all the animals inoculated, the severity of the lesions varying, of course, according to the virulence of the organisms injected, but always exceeding that seen in the human subject. All the tissues of the eye except the lens were proved to be capable of infection.

In his second series of experiments Finnoff used dead bacilli in the same way, and produced eye lesions in forty-two out of fifty-nine animals. The dosage varied from 0.2 to 10 mg. of bacilli, but curiously enough the size of the dose had no influence on the nature of the lesion or the frequency of the "takes." The author does not attempt to explain this, but possibly if the dose had been reduced further a difference would have been noticed. He also omits to mention whether there was any evidence of pre-existing tuberculosis in the animals he injected, but if there was none it is interesting that apparently active lesions of a tuberculous nature could be produced by injections of dead bacilli in uninfected animals. Finnoff does not emphasize this point himself, but it seems to me to be of importance in showing that some of the supposedly tuberculous lesions we are discussing may be toxic and allergic rather than embolic in origin.

Since Finnoff's work other experiments of a similar type have been performed; thus Ohmart⁵ injected 0.02 c.cm. of a dilute suspension of tubercle bacilli into the ciliary bodies of fifteen rabbits and produced tuberculous lesions. In addition to the usual tuberculous changes Ohmart found vitreous opacities, some of which had the structure of a tubercle, and perivascularitis, in which the extension came apparently from the vitreous rather than along the perivascular lymph spaces. It is perhaps notable that four of the animals were made hypersensitive by a previous introduction of tubercle bacilli into other parts of the body, and that in these animals the disease was more widespread and ran its course more rapidly.

Another interesting investigation on the same lines was carried out by O'Rourke,⁶ who found that certain extracts of the tubercle bacillus when injected into the carotid artery of rabbits were sufficient to produce epithelioid tubercles of the eye with or without giant cells. Those which brought this about were the lipin proteins extracted from tubercle bacilli by petroleum ether or by alcohol. The residue, so-called defatted tubercle bacilli, was extremely toxic, killing most of the rabbits and producing in those that survived violent inflammations of the eye in no way resembling tuberculosis. Experiments such as these prove that the tubercle bacillus can infect the eye, and that in some cases the infection may run a relatively benign course.

Eye Involvement in Tuberculosis

When it comes to investigations the other way round the problem is more difficult. One would expect to get some help from the figures giving the incidence of eye disease at tuberculosis sanatoria. When such figures are examined, however, the result is rather surprising. Thus

Goldenburg,⁷ in examining 1,073 cases of authenticated tuberculosis, found only seven showing disease of the iris in an active or healed state, and only nineteen with fundus changes that could seriously be considered as tuberculous. The same thing seems to be true of hospitals for the treatment of surgical tuberculosis. In one of these no eye lesions had been found at all, and in another, during the last twenty years, only one case of iridocyclitis had been seen. Evidence such as this would seem to make it improbable that the Continental view as to the frequency of tuberculosis can be the correct one. Goldenburg's explanation that the eyeball has no true lymphatics and can therefore be infected only by the blood stream or by direct continuity may be the correct one, but it does not tell us why so many cases of eye disease are thought by responsible people to be tuberculous.

Among such people the most eminent and persuasive is probably Professor Meller, and anyone who heard or has read his Doyne Memorial Lecture⁸ cannot fail to have been impressed by it. Meller was led to his theory by the observation that many cases of spontaneous uveitis were unexpectedly improved by a course of tuberculin. He then set about looking for signs of tuberculosis in other parts of the organism, and in an x-ray examination of the chest was able to make out changes indicative of existing or past lung infection. At the same time, Löwenstein's method of obtaining cultures showed that there were tubercle bacilli in the blood in 14 per cent. of 132 cases of spontaneous uveitis. The low percentage is explained by the supposition that the bacillaemia is present only for a short time, so that the examination must be made during this period if the bacteria are to be found. Löwenstein also showed that tubercle bacilli could be found in the blood of clinically healthy people, an observation which explains why supposedly tuberculous eye infections can develop in otherwise healthy individuals.

The crowning proof, however, of the tuberculous nature of spontaneous uveitis is furnished by the occurrence of focal reaction in the eye after the injection of tuberculin accompanied by general symptoms. Such a reaction, when it occurs, seems to be irrefutable evidence of the tuberculous nature of the eye disease. Lagrange,⁹ after considering various skin and other tests, concludes that, short of biopsy, this is the only certain method of establishing the diagnosis. I sometimes wonder, though, if the method is so certain, particularly in view of Finnoff's work, already mentioned, in which he produced eye lesions by injections of admittedly large doses of dead tubercle bacilli.

Meller's views on sympathetic ophthalmitis are probably well known. Briefly, what he suggests is that an injured eye furnishes a *locus minoris resistentiae* in which circulating tubercle bacilli can find a nidus and develop; then, having become, as it were, conditioned to the uveal tissue of one eye, they can pass to the other and grow there.

Skin Tests in Diagnosis

So much for Meller's views; what other evidence can we get that a case of obscure eye disease is due to the tubercle bacillus? First, there are the skin tests, of which the Mantoux is the best known. There are others here who are better qualified than I am to deal with this subject, so I do not want to say more than record what I believe is the general opinion—namely, that a positive Mantoux in an adult has very little diagnostic value.

Verne's test has been used by us a good deal recently at St. Mary's Hospital. It is an empirical reaction founded on the unexplained observation that a precipitate is formed if serum containing tuberculous antigen be mixed with a solution of resorcin. Unfortunately there are some fallacies in the test, of which the most important

is that if there should be pyrexia within twenty-four hours of taking the patient's blood a precipitate will form even in the absence of tuberculosis. A negative Verne is therefore said to have more value than a positive one. The test is, I think, of use; at any rate in a series of cases of iridocyclitis, choroiditis, and retinal haemorrhage at St. Mary's, in which Dr. Mummery kindly performed it, the result was uniformly negative and the patients all improved as a result of elimination of focal sepsis, administration of streptococcal vaccine, etc. As a control we sent a specimen of blood from a patient with an obviously tuberculous iridocyclitis with massive keratic precipitates, corneal haze, and a history of painless apyrexial parotid swelling three weeks before admission. X-ray examination of the chest showed large hilar glands, though there were no clinical signs of phthisis. In this case the result was strongly positive, and the Mantoux test was negative, though possibly it would have been positive if a stronger solution of tuberculin had been used.

A criticism of the Verne test is that it may not be sufficiently delicate, by which I mean that although it will show the presence of tuberculous antigen in the blood, this has to be a certain titre before a positive result is obtained. An example is furnished in tuberculous meningitis, when the blood may give a negative result, whereas the cerebro-spinal fluid is positive, although the infection must have been primarily blood-borne. On this analogy I feel it would be worth while to examine the Verne reaction of the aqueous humour obtained from a case of apparently spontaneous uveitis, but I have not yet had an opportunity of doing this.

Effect of Treatment with Tuberculin

The effect of treatment with tuberculin might be thought to throw some light on the aetiology, but here again there are several fallacies. First, there is the inherent tendency of the patient to get well when allowed to rest and enjoy good food and surroundings. Secondly, there is the possibility that the immunity is not always specific, and that administration of tuberculin will increase the patient's resistance to organisms other than the tubercle bacillus. This is shown clinically by the relative absence of pyogenic infections in tuberculous sanatoria.

In a paper published a few years ago¹⁰ I quoted a letter from Dr. Houghton of Colindale Hospital (a hospital which has 350 beds devoted entirely to pulmonary tuberculous cases of all ages), in which he said that he had seen in the previous four years no acute infections attributable to the common organisms, except in cases in which the diagnosis of tuberculosis had not been confirmed. He also said it was a common experience to find that, in cases of tuberculous empyema in which a rib had been resected and in which eventually a secondary infection had developed, the activity of the tuberculous process subsided. Such cases, when treated with tuberculin, gave encouraging results with regard to healing of the sinus. I spoke to Dr. Houghton recently on this subject, and he tells me that what he said four years ago still holds true. Another observation of the same kind was made to me during an influenza epidemic by the medical officer of a sanatorium. He told me that not one of the patients had contracted influenza although several of the visitors to the sanatorium were afflicted.

From the test tube point of view the same kind of thing seems to be true, as is illustrated by one of Sir Almroth Wright's experiments.¹¹

He took a series of capillary tubes and into one of them drew 10 c.mm. of a broth suspension of staphylococci, then ten separate c.mm. of blood. The first c.mm. would obviously get the heaviest dose of staphylococci and the succeeding ones progressively less, so that he had in his tube a series of

ten separate c.mm. of blood implanted with a gradually diminishing number of staphylococci. This tube was used as a control, and contained untreated blood. In a second tube the blood had been previously inoculated with a small dose of tuberculin, and in a third with a larger dose. Wright has already shown that *in vitro* the immunizing response to a vaccine is instantaneous, and we have, therefore, in these three tubes something comparable to thirty patients, of whom the first ten have a diminishingly severe staphylococcal infection, the second ten a similar series of infections, but also a small dose of tuberculin, and a third a larger dose. By a special technique, which need not be detailed, it was possible to find out the numbers of staphylococci which survived in each c.mm. of blood. In the case of the heavily implanted bloods the effect of the small dose of tuberculin was to reduce the number of surviving organisms by 50 per cent. as compared with the control, whereas the effect of the large dose of tuberculin was exactly the reverse, the number of surviving organisms being double the number left in the control blood. In the lightly implanted bloods the large dose of vaccine enhances the bactericidal power more than does the small one.

It is therefore important to determine the correct dose of tuberculin, and Wright has recently worked out a method of doing this which is not yet published. The result of its application is convincing, and he has kindly allowed me to quote a case in which it was used. Before injection the patient's leucocytes phagocyted an average of twelve staphylococci per 100 cells; three hours after intravenous injection of the calculated optimum amount of tuberculin phagocytosis had gone up by nearly 1,000 per cent., the number of organisms per 100 cells being 118. In the face of such a result there will be a few who would disagree with Sir Almroth's suggestion that in cases of undetermined infections a passionate conviction that immunity is specific should not hold us back from inoculating minimal doses of tuberculin B.E., or, in cases associated with rheumatoid changes, a vaccine of intestinal streptococci.

What tests are we left with then? First place must, I think, be accorded to the occurrence of a local and a general reaction following the injection of tuberculin, though the theoretical objection to such a test is obvious—namely, that one may make the patient worse. In practice, however, I doubt whether such an objection is valid, because in the few instances in which I have obtained the reaction, although there was a temporary exacerbation of symptoms, the ultimate result was favourable. The following two cases illustrate this.

A woman aged 49 had had recurrent iritis since the age of 17, and was under the care of Mr. Paton. Both irides were almost completely bound down. There was a history of a past attack of iritis with raised tension and pain, and active iritis was present in both eyes. No septic focus was found, so she was given milk injections and intensive salicylate treatment with little effect. I saw her several times during Mr. Paton's absence on holiday, and ordered tuberculin B.E. The first dose of 1/100,000 mg. produced no effect, but the second, of 1/75,000 mg., produced some chills and a little pain in the eye. The dose was therefore reduced and worked up more slowly until both eyes were white and double iridectomy could be performed without any complications.

The second case was that of a doctor aged 50, who had angioid streaks and retinal haemorrhages. The left eye, after going through a stage of retinitis circinata, developed a plaque of fibrous tissue over the macula, central vision diminishing to less than 6/60. The blood calcium and the coagulation time were normal, and administration of iodine and an autogenous streptococcal vaccine was of no avail. Just at the time the left eye failed the right began to show signs of going the same way, haemorrhages developing in the macular region. Vision, however, remained good for a further six months and then began to fail. Mantoux's test was positive, so tuberculin injections were given, and the haemorrhages slowly disappeared. Vision is even now only 6/24 one letter, but at one time it was down to a doubtful 6/60, so some improvement can be claimed; and as the haemorrhages have gone it may be hoped that there will be no further deteriora-

tion. I cannot be sure about the occurrence of a local reaction in this patient after tuberculin, but there was no doubt about a slight general reaction, the temperature rising to 100° F. on at least one occasion.

How the Bacillus Acts

I could tell you of other cases in which the condition has improved after treatment with tuberculin, and of yet others which have not improved until this treatment was supplemented by general hygienic measures—for example, residence at the Royal Sea Bathing Hospital, Margate—but I want to pass on now to consider the question of how the tubercle bacillus causes these obscure diseases, if, indeed, it does.

There are three possible methods: (1) By actual lodgement of the bacillus. (2) By diffusion of its toxins, via the lymph or blood stream. (3) By some allergic reaction.

With regard to (1), the tubercle bacillus is notoriously difficult to find; it has never yet, so far as I know, been discovered in phlyctenules, but now and again it has been found in the eye—for example, Gilbert¹² found tubercle bacilli in the perivascular sheath of a retinal vein in an eye excised for perivasculitis. It is suggested¹³ that in such cases the infection enters the eye as an embolus into the ciliary body and spreads to other parts by way of the ocular fluids. The bacilli are not, so to speak, naked and unadorned, but are surrounded by clumps of epithelioid and giant cells, whose sanctions have proved ineffective against the aggressor still living in their midst. Such cases are perhaps outside the scope of our present discussion, because they represent what might be termed "honest tuberculosis of the eye," in which the infection steadily progresses until the eye is lost. It is, however, open to argument that if bacilli can be found in a severe case of recurrent retinal haemorrhages they may also be present in a less severe case, particularly if the patient's immunity is higher. If Löwenstein's findings are verified—namely, that tubercle bacilli can be found in the blood of clinically healthy persons—it makes the hypothesis of actual lodgement of the bacillus much the most likely one.

It is difficult to be at all definite concerning the toxæmia theory. Certainly Finnoff's experiments with dead tubercle bacilli would seem to show that such a thing is possible, and we have also the local reaction which occurs after an overdose of tuberculin. On the other hand it does not follow that because such changes occur experimentally they occur clinically, and histological methods will need further refinement before we can exclude absolutely the presence of the tubercle bacillus itself somewhere in the eye.

With regard to allergy or hypersensitiveness, this should play a part whichever of the first two theories is correct. While immunity is the state which produces reactions leading to the death of the bacillus, allergy is the state which determines the response of the tissues to the protein liberated by the breakdown of the bacillus. It was for some time considered that the two processes were part and parcel of the same thing, and that if allergy was abolished or diminished immunity was proportionately affected. That this is not so has been strikingly shown in a series of papers published by the Johns Hopkins Hospital.¹⁴ In one of these an account is given of a group of guinea-pigs which were inoculated in the groin with a milky suspension of avirulent tubercle bacilli, the animals becoming, after the lapse of a few weeks, relatively immune to reinfection with virulent organisms. At the time this immunity was established evidence of allergy to tubercle bacilli and their protein products became manifest, and half the group were given daily injections of tuberculin O.T., which were continued in increasing amounts until all evidence of the allergic state had disappeared.

When this had been achieved both groups and normal non-immunized controls were given injections of virulent tubercle bacilli into the anterior chamber. The normal controls after a latent period developed tuberculous iritis, which progressed with great rapidity through caseation of the anterior segment to rupture and disorganization of the eye. The immune allergic group developed an intense inflammatory reaction within two days, the severity and duration of which varied with the dosage of organisms. This was followed after several weeks by slowly progressive kerato-iritis, which in only a few eyes went on to complete caseation. In an equally small number no progressive ocular disease became evident at all. In the immune desensitized group the initial allergic reaction was entirely absent; a large number developed no clinically recognizable ocular lesion, while the lesions which did develop in some were less severe and progressed more slowly than in the immune allergic group. There is thus no evidence that the loss of allergy deprives the immunized animal of any aspect of his immunity. In fact it is the other way round.

This has also been shown by some tissue culture experiments carried out by Rich and Lewis.¹⁵ They placed thoroughly washed fixed tissue and blood cells of allergic and of normal guinea-pigs in the plasma of normal and of allergic animals, and the same amount of tuberculin was added to all the cultures. The cells of the allergic animals were regularly and promptly killed, regardless of the plasma in which they were placed, while the cells from normal animals remained alive and multiplied when exposed to the same concentrations of the tuberculin that killed the allergic cells. It is justifiable, therefore, to regard hypersensitiveness as a change in the body cells whereby the relatively bland products of the breakdown of tubercle bacilli are converted into powerful irritants and poisons without any apparent gain to the organism in the way of immunity. It would seem that a good case can be made out for allergy or hypersensitiveness being one of the factors producing inflammatory reactions and tissue destruction in the presence of tubercle toxin, and in this sense the administration of tuberculin may be of service not only in increasing the patient's immunity but in diminishing his allergy to tubercle protein, as in the case of the guinea-pigs at the Johns Hopkins Hospital.

If there is such a thing as obscure disease of the eye due to the tubercle bacillus it would seem reasonable to suppose some sequence of events such as this. Most adults harbour a healed focus of tuberculosis somewhere. As a result, say, of extreme exhaustion, this focus lights up, the tubercle bacilli are disintegrated because the patient has acquired immunity, and in their disintegration they set free tuberculoprotein. Unfortunately the patient is also hypersensitive, and therefore develops an allergic tuberculotoxic lesion of the eye.

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