

THE OPHTHALMO - REACTION

to

TUBERCULIN

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THE OPHTHALMO - REACTION TO TUBERCULIN

TO state that the early diag^{nosis}~~nosis~~ of tubercle is often a matter of extreme difficulty is to state a fact known to every physician. Even when well developed tuberculosis of the viscera and of the nervous system is often obscure, and the most prominent symptoms often point to disease of other organs than the organ affected.

In the case of pulmonary tubercle, the decisive sign, the presence of bacilli in the sputum, is as a rule of no assistance in early diagnosis, for it is well-recognised that foci, large enough even to produce physical signs, may exist long before bacilli, after repeated careful examination, are found in the sputum, the pathological condition being of such a nature and so situated that the bacilli, present and active, do not find their way into the expectoration. In children, too, and in some women, the sputum is regularly swallowed, and this sign is not available.

Again, even where physical signs are marked, a differential diagnosis is often difficult, and sometimes, if one relies solely on physical signs, impossible, to make. Chronic pneumonia in children is often wrongly diagnosed as a tuberculous condition, which, in general symptoms and temperature it strongly resembles. Much rarer conditions affecting the lung, liable to be mistaken for tuberculosis are pneumokoniosis

syphilis, actinomycosis, echinococcus and new growths.

More evident lesions, where bones, joints or glands are affected, present often to the surgeon the same difficulty of diagnosis.

The overwhelming importance of the earliest possible recognition of tubercle is universally admitted, the consensus of opinion being that cases recognised sufficiently early and placed under suitable climatic and hygienic conditions, may completely recover. Every pathological anatomist frequently finds cicatricial patches, or calcareous deposits in the lung, evidences of healed tuberculosis, the process of healing, too, having received no aid in many cases from specific treatment. To wait for definite symptoms and well-marked physical signs is often to find later that the disease has progressed too far for successful treatment.

The wide prevalence of this disease, the frequent difficulty of its early detection, and the fortunate results following early diagnosis and treatment in most cases, have led to the introduction of special methods of diagnosis.

One of the first of these was the subcutaneous injection of "tuberculin". This substance, introduced by Koch, is "a glycerin extract of cultures of the tubercle bacillus." Small doses must be used, the tuberculin for subcutaneous injection being suspended in a .5 per cent solution of carbolic acid. According to Latham,¹ if the patient is delicate, an

amount of this fluid containing a milligramme of tuberculin is to be injected into the back or buttock. In the tuberculous, the injection is followed by malaise and rise of temperature. If this reaction has not taken place in three days, a dose of 2 milligrammes is given, and, no reaction being obtained after another interval of three days, three mgms. given. If this dose fail to produce a reaction within three days, the patient may be pronounced free from tubercle. For ~~most~~ ^{more} robust patients, the initial dose may be up to 5 mgms., followed by doses up to 10, and 20 mgms.

But this method has serious disadvantages. Its sphere is limited to non-febrile cases. It requires the confinement of the patient to bed or to the hospital ward, and the careful taking of the temperature at frequent intervals. It must be applied with graduated doses, - for an excessive dose may give a reaction in a non-tuberculous case. Its necessary repetition therefore makes it terrifying to children, and unpleasant to adults. Further, there is a danger of lighting up a tuberculous focus, a danger which is all the greater from the fact that as a result of the general reaction, the resisting power of the body is lowered.

For these reasons, the subcutaneous injection of tuberculin, though becoming more and more extensively used in cattle, ²⁴ has been almost entirely given up in man.

In May.1907,Von P²erquet,in communications read before the Berlin Medical Society,introduced a novel method of using tuberculin for diagnostic purposes. A few drops of diluted tuberculin having been placed on the scarified skin,as in Jennerian vaccination, a small papule appears, in a tuberculous subject,at the point of inoculation, within forty-eight hours, and lasts some eight hours. This reaction to tuberculin,known as the "cuti-reaction", Von P²erquet asserted to be only rarely obtained in the healthy subject. Further investigation showed that reliance could only be placed on this test in the case of young children,as most adults gave the reaction,and further,a positive reaction could be obtained both in active and in cured cases of tuberculosis. The cuti-reaction was pronounced by several observers to be not sufficiently reliable for use in diagnosis.

Wolff-Eissner of Vienna,while investigating Von P²erquet's discovery,found that if the tuberculin,in a 10 per cent solution,were placed ~~on~~^{va} the conjunctiv~~am~~ of animals, a conjunctivitis,accompanied in some cases by a feeble general reaction,resulted. Vallée applied this discovery to the diagnosis of tubercle in cattle,proving its value for that purpose,but thought that the sever^e symptoms rendered it unsuitable for use in the human subject.

Professor Calmette,of Lille,introduced a modification

of this method, suited for use as a means of diagnosing tubercle in man. Calmette named his method the "ophthalmo-reaction to tuberculin". Describing his method (La Presse Medicale, June 19th., 1907) Calmette says that in order to avoid the irritating effect of glycerine on the conjunctiva, he used dry tuberculin, precipitated by alcohol at 95^o, dissolved in sterilised, distilled water. The strength of the solution was 1 per cent, and it was always freshly prepared. A drop was placed in one eye. Five hours after the instillation, sometimes in three, all the tuberculous cases showed a marked congestion of the palpebral conjunctiva, which became bright red, while the caruncle became swollen, reddened, and covered with a light fibrinous exudation. The injection of the vessels became gradually more pronounced, and was accompanied by lachrymation. The maximum reaction took place in from six to ten hours. No pain was complained of, vision was only slightly interfered with and the temperature was not appreciably affected. The intensity of the reaction could be conveniently estimated by comparison with the eye into which no tuberculin had been placed. In infants at the end of eighteen, and in adults, twenty-four, or thirty-six hours, the signs became less marked and disappeared. In healthy persons, or in those suffering from non-tuberculous affections, the instillation of tuberculin into the eye produced no effect, or at the most, in from one and a half to three hours afterwards,

a slight redness was seen, which quickly disappeared, and was not accompanied by fibrinous secretion or lachrymation.

Calmette tried the method on 25 persons, of whom 16 were definitely tuberculous, and 9 had non-tuberculous diseases. Each of the 16 tuberculous cases gave a positive reaction. In one of these, before the instillation, tuberculosis was not suspected, but was proved afterwards. The 9 non-tuberculous cases gave no reaction: their diseases were Sciatica, Bright's disease, tabes, lymphangitis, mitral incompetence, insanity, cerebro-spinal sclerosis, influenza and acute rheumatism.

Calmette claims for the method that it is one of great delicacy, that it deserves to be studied by clinicians, being easy of application, more prompt in its results than the cuti-reaction, causing no lasting discomfort nor pain, and, so far as experience goes, presenting none of the inconveniences or dangers of the subcutaneous injection of tuberculin. Physicians will find it, he considers, a simple, delicate, and rapid method of diagnosing obscure cases of early tubercle or of proving the cure of old tuberculous lesions.

In an article a month later,⁵ written in collaboration with Breton, Painblan and Petit, Calmette describes the results of trials of the method in 115 cases, and the experiences of some other observers in altogether 321 cases. He

found that all the tuberculous cases, children and adults, gave a positive reaction. Some patients under treatment for non-tuberculous affections also gave a reaction. On more thorough examination, "nearly all" of these patients were found to have suspicious glandular or pulmonary lesions. Calmette and his confrères conclude that evidently the ophthalmo-reaction method allows in many cases an early diagnosis to be made, that it always gives a positive indication of a tuberculous lesion, be it in bone, gland, viscus, meninges or lungs.

They found that in some cases reaction was delayed, appearing in 12 or 24 hours after instillation, and disappearing in about 72 hours, in some cases even later. These late reactions might be as intense as the early.

No relation could be shown to exist between the intensity of the reaction and the gravity of the lesion, those suffering from simple tuberculous glands giving often a more marked reaction than cases of pulmonary tubercle with cavity formation.

Calmette's previous conclusions were confirmed -- there was no pain, no lasting interference with vision, no temperature or general reaction, while the tuberculous lesions remained unchanged for better or worse. The method was absolutely harmless.

They considered that the test ought not to be

employed in cases where there is disease of the eye or eyelids, because its diagnostic value would be lost, and there would be a danger of aggravating a pre-existing microbic infection.

Briefly noted, the following are some of the results of trials of the method and opinions expressed by observers.

⁶
Letulle tested 75 cases considered to be tuberculous. Of these 72 gave a positive reaction, two of the three negative cases being moribund. His opinion was extremely favourable.

⁷
Sydney Stephenson, contrary to the opinion of Calmette and his co-workers, found the method of great value in diseases of the eye, especially in cases of diseases, such as chronic irido-cyclitis, some forms of choroiditis, and scleritis, which are held by some authorities to be of a tuberculous nature, and by others to be non-tuberculous. Testing 6 cases of Phlyctenular conjunctivitis and keratitis, affections which have for years been suspected to be of tuberculous origin, Stephenson obtained a positive reaction in all. Three cases of choroiditis, with no history or sign of syphilis, two cases of chronic irido-cyclitis, and one case of tubercle of the iris, gave positive reactions. Of 8 cases of interstitial keratitis, three gave a positive

reaction, the remaining five, all giving a negative reaction, had well-marked signs of congenital syphilis .

Austin and Grünbaum⁸ tested 70 cases. Of these 20 were thought to be tuberculous, and of the 20, 18 gave a positive reaction, one of those who failed to give a reaction being moribund, a condition in which a reaction, as previously noted by Letulle, is not obtained. 52 gave no reaction: these suffered from various non-tuberculous affections. Austin and Grünbaum concluded that the ophthalmo-reaction promised to be a most valuable method of diagnosing obscure cases of tubercle, but was not infallible.

Cohn,⁹ from an examination of 310 cases, concluded that "a positive reaction renders a diagnosis of tubercle highly probable, but a negative result does not exclude that disease, since 50 per cent of severe cases of pulmonary tuberculosis fail to react."

Comby⁹ of Paris, applied the test to 300 children. With the 1 p.c. solution he had severe after-effects, and he therefore reduced the strength to $\frac{1}{2}$ per cent, with favourable results, no reaction following in non-tuberculous cases, while in the tuberculous he obtained a reaction after each application. He considered the method one of great practical value in the diagnosis of obscure cases of tubercle.

Maclennan of Glasgow, obtained occasionally, like Comby, an over violent reaction and was of opinion that a solution of $\frac{1}{2}$ per cent was sufficient for a preliminary application. Of 25 cases known to be tuberculous, 23 gave a positive reaction with a 1 per cent solution. The two failing to give a reaction were a child who cried as the application was made, thus washing out the drop of solution, and a case of sorofuloderma. Of 12 suspected cases, 9 gave a positive reaction. With a strength of $\frac{1}{2}$ per cent, of 20 known tuberculous cases, 19, and of 20 cases apparently free from tubercle, 4, reacted.

Maclennan does not agree with Calmette that the presence of glycerine or carbolic acid in the tuberculin interferes with the reliability of the test, proving his contention by finding that these substances in the same strength as in the solution used have no effect on the healthy eye. He concludes that "for the most part Calmette's claims are fully justified," that "the test apparently reveals the presence of tuberculous lesions that are quite benign and unsuspected from a clinical point of view, as well as those that are more obvious."

//

Webster and Kilpatrick of Mount Vernon Hospital for Consumption, report having tried Calmette's method in 43 cases of pulmonary tuberculosis, all of whom gave the reaction. Of 58 cases in whom it was thought (judging from the

temperature chart and the fact that no tubercle bacilli had recently been found in the sputum) that the disease was quiescent, 36 reacted, and of 16 suspected cases, without definite physical signs and without expectoration or with no tubercle bacilli in the sputum, 6 reacted. These writers obtained a rise of temperature in 7 cases, unaccompanied by headache or malaise. The local reaction in these cases was not so severe as in some of the others. The temperature charts of two of the seven patients are shown in the article: in one case the rise of temperature is from 100° to 101° and in the other from 99° to 100°. As the charts show that both patients had before instillation a moderate pyrexia, little importance can be attached to the fact that a slight rise of temperature took place shortly after the application of the tuberculin.

Commenting on these results, Squire, of the same hospital, expresses the opinion that "Calmette's method certainly seems the best for diagnostic purposes yet suggested".

12 14

Audeod at Geneva Children's Hospital, tested 31 cases. Of 13, decidedly tuberculous, 12 reacted, the failure being a case of cutaneous tubercle after curettage; of 3 suspicious cases, one reacted, and of 15 non-tuberculous cases, all gave no result. Audeod considers the utility of the method proved especially for suspicious cases.

13.

Green found that some advanced cases gave no

reaction, while some very early cases gave a marked reaction. He mentions two cases in which he found Calmette's method of very great service. One was a patient of 48 with a swelling of doubtful nature in the neck, who gave a marked reaction. The diagnosis of tubercle then made was ultimately verified. The other case was that of a patient with an ulcer on the chin which looked tuberculous, and here the absence of the ophthalmo-reaction aided to a correct diagnosis.

¹⁵
Eyre, Wedd and Hertz, of Guy's Hospital, formed a "distinctly favourable opinion" of the method, after applying it in 138 cases. Of this total, 63 gave a positive reaction; the majority of these were "unquestionably tuberculous", and, "more important still" these observers did not note "a definite reaction in any cases in which the absence of tubercle has been conclusively proved". 75 cases were unaffected: of these 17 were apparently healthy, 12 were doubtful, with tuberculosis a possibility, and 46 suffered from various non-tuberculous^{ov} diseases. The positive cases suffered from phthisis pulmonalis, spinal caries, tuberculous peritonitis, adenitis, arthritis, lupus, Addison's disease, and tubercle of the kidney. They found that the reaction could not be obtained during the last week of life, even in undoubtedly tuberculous cases.

¹⁶
Dr. Boyd of Edinburgh, describes some interesting

cases in which he tested the value of the ophthalmo-reaction. One was that of a girl of 18, diagnosed as chlorosis. On admission to hospital, she was anaemic, but the colour index was normal. She was considerably emaciated, with some night sweating and a slight evening rise of temperature. Some distention of abdomen, with resistance, gave rise to a suspicion of abdominal tuberculosis. The ophthalmo-reaction was positive. Tuberculous Peritonitis with ascites subsequently developed. Other cases were Addison's disease, tuberculous mesenterica, tuberculous disease of spine with spastic paraplegia. In these a positive reaction was obtained, while no reaction followed in all the control cases, when the patient obviously had no tubercular lesion.

Heywood,¹⁸ of Manchester, thought a .5 per cent solution for children strong enough, even that strength in some cases giving a too violent reaction. He "had up to the present (Feb. 29, 1908) seen no case which gave a positive reaction where tuberculous disease was not found post-mortem". One of his positive cases was that of a child who at the time had no evident signs of tuberculous disease, but who later developed a chronic pleurisy.

Many other observers have published their experiences of the method in limited numbers of cases and have expressed a favourable opinion of its value in diagnosis.

While the majority of writers approve of Calmette's method and assert the absence of untoward after-effects in their

experience, adverse criticism is not wanting, and several writers have published cases where the instillation of tuberculin was followed by a local condition which gave rise to some anxiety.

¹⁹ Woodcock, of Leeds, after investigating 100 cases, found that some cases of severe tuberculous infection did not give a positive reaction, while a reaction was sometimes obtained in people who had clinically no tuberculous disease. As a means of diagnosis he preferred the "inoculation of a blistered surface".

²⁰ Kremes of Vienna, after a series of comparative observations, came to the conclusion that the cuti-reaction of Von Perquet was "more trustworthy, easier, less severe, and less painful". In four of his cases the eye was severely affected for days. He used a l.p.c. solution.

¹⁷ Walker, of Leeds, has referred to the possibility of infection or injury to the eye. One of his positive cases developed in a few days a phlyctenulae corneal ulcer which healed rapidly without leaving a scar. This case and a similar case observed by Webster and Kilpatrick, were the only cases known to the writer.

¹⁸ Heywood of Manchester, had one case in which the conjunctivitis lasted for six weeks.

Maitland Ramsay, of Glasgow has reported a case "to show that the ophthalmo-reaction must be used with caution and discrimination." The patient, a girl of 12 years, suffered from superficial vascular ulceration of the right cornea. The left eye had been similarly affected two years previously, and there was enlargement of the cervical, and submaxillary glands, but no sign of pulmonary tuberculosis could be detected on careful examination. One drop of a 1 per cent solution of tuberculin was instilled into the left eye. "Within 24 hours there was violent muco-purulent reaction, the discharge being very abundant and accompanied by marked swelling of the lids and thickening of the palpebral conjunctiva." The condition was uninfluenced by treatment, and at the end of six weeks the eye was still discharging. The condition then began to steadily improve, but a central corneal opacity with serious impairment of vision, was left.

Mackay reports a case of a woman whose complaint was diagnosed as tuberculosis of left knee. An expert to whom she was sent for confirmation of the diagnosis instilled a drop of a 1 per cent solution of tuberculin in the right eye. Photophobia, lachrymation and gumming of the eyelids soon followed, the symptoms only subsiding after ten days' treatment with boric acid lotion. There was a

recrudescence some three weeks later and more than ten weeks after the instillation, she had still a red conjunctiva and slight photophobia. The other eye remained unaffected.

²²
Allen mentions the occasional occurrence of a severe reaction while using Calmette's method in ophthalmic work, but considers that if a $\frac{1}{2}$ per cent solution is used instead of a 1 per cent, and one drop only of the solution placed in the eye, undesirable results will not ensue.

During the past ~~weeks~~^{winter} I have tested the method, applying it in 120 cases. The tuberculin, in a dry state, was obtained from Mr. Jos. Flash, the London Agent of Poulencq Frères, of Paris, and the solution was prepared with sterilized distilled water not more than a few hours before being used on a batch of cases. For adolescents and adults a 1 per cent solution was used, and for young children a $\frac{1}{2}$ per cent. To avoid any error that might arise from the slight transient signs of irritation, referred to by Calmette, ensuing in some eyes, the presence or absence of reaction was judged from the condition of the eye in 24 hours after instillation.

In the positive cases, the reaction began in four or six hours after the instillation of one drop of the tuberculin solution into the lower conjunctival sac. A feeling of "sand" or "grit" in the eye was the first symptom noticed by several of the patients. The lower

palpebral conjunctiva became congested, the caruncle swollen and reddened, the vessels of the bulbar conjunctiva injected, with lachrymation and the appearance of mucofibrinous secretion. This describes the usual condition in all the positive cases, though some showed the symptoms more markedly than others. No pain, malaise, or headache was complained of. In the majority the signs had practically disappeared in 48 hours: in some there were still some signs of conjunctivitis on the 3rd or 4th day. There was no relation between the gravity of the lesion and the severity of the reaction: cases of tuberculous adenitis or a small patch of cutaneous tubercle gave as decided a reaction as a well marked case of pulmonary phthisis.

In only one case did the after effects give rise to any anxiety. This was a little girl of 3 years, who had a tuberculous ulcer below the angle of the jaw, and a tuberculous glandular abscess further back, lesions which had just been actively treated surgically when the instillation was made. One drop of a $\frac{1}{2}$ per cent solution was used, and 24 hours later, the whole conjunctiva was infected, lachrymation was profuse, and there was some muco-purulent secretion at the inner canthus. After the fourth day the condition was treated with boric acid lotion, but remained unchanged

for seven days in all, beginning then to improve, the signs disappearing by the twelfth day. The condition did not fortunately seem to give the little patient any pain whatever.

Of the 120 cases tested, 40 were definitely diagnosed as, or suspected to be, suffering from tuberculosis: 30 were adults and 10 children. Of the 40, 38 gave a positive reaction. 80 were apparently either in normal health, or considered to be suffering from non-tuberculous diseases. Of the 80, 34 were children, and 46 adults. Of the children 4 gave a positive reaction, all the adults were negative, a few having a slight injection shortly after instillation, but no signs 24 hours after instillation.

CASES IN DETAIL

Adults thought to be tuberculous
A Giving a positive reaction.

NAME	SEX.	DISEASE	DIAGNOSED BY
1 R	m	Phthisis Pulm.	Physical signs T.B. in Sputum.
2 Matthews	m	" "	Physical signs.
3. Mortell	m	" "	P. signs T.B.
4 Mowell	m	" "	Es. T.B.
5. D	f	" "	Physical signs
6 S	m	" "	" T.B.
7 H	f	" "	" T.B.
8 C	m	" "	P. signs T.B.
9 B	m	" "	T.B. sputum
10 C	f	" "	P. signs
11 T	f	" "	"
12 P	m	" "	"
13 L	f	" "	"
14 C	f	" "	"
15 M	m	" "	P signs
16 C	m	" "	"
17 W	f	" "	"
18 H	m	" "	"
19 K	f	Cut. tubercle	Appearance etc.
20 J	m	Spinal cases	Physical signs
21 B	f	Phth. Pulm.	" "

22	L	m	<i>Phth. Pulm.</i>	<i>Physical Signs.</i>
23	T	f	Phth Pulm	Physical signs
24	C	f	Lupus face	History etc
25	W	m	Tub. elbow	History etc
26	B	m	Tub. glands	"
27	F	m	" "	"
28	S	m	Phth. Pulm.	Phys signs.
B. giving a negative reaction.				
29	B.	m	Phthisis Pulm.	^{T.B.} Physical signs
30	B	m	Sacr ^o iliac disease	Signs and symptoms

CHILDREN thought to be tuberculous

31	C	m	aet 6	Phth. Pulm.	Phys signs
32	M	f	aet 10	" "	" "
33	H	f	aet 14	" "	" "
34	M	m	aet 9	Tub. Adenitis	Signs etc history
35	W	m	aet 3	Tabes mesenterica	Signs History
36	P	m		Tub. adenitis	" "
37	R	f	aet 3.	Tub. adenitis	" "
38	S.	m	aet 12	Tub. adenitis	History signs etc
39	H	f	aet 5	Cutaneous tub.	" " "
40	H.	f	aet 12	Tub. adenitis	" " "

Severe reaction.

ADULTS UNDER TREATMENT FOR SLIGHT INJURIES ,OR AFFECTIONS
 CONSIDERED NON-TUBERCULOUS.

1.	M.	m	Injury
2.	W	m	Carcinoma larynx
3.	H	m	Tonsillitis
4	K	m	"
5	G	m	Influenza
6	C	m	Injury
7	W	m	Influenza
8	S	m	"
9	H	m	"
10	T	m	Injury
11	S	fem	"
12	A	m	"
13	H	fem	"
14	M	m	Chr. Bright's.
15	E	f	Injury
16	P	f	Normal health
17	M	f	Chr. Bronchitis
18	H	m	"
19	H	f	Chr Bright's
20	R	m	Arterio-Sclerosis
21	M	f	morbus cordis
22	P	f	"

23	M	m	Emphy ^s ema
24	S	f	Carcinoma of Stomach
25	G	f	" " uterus
26	T	f	Asthma
27	F	m	Axillary abcess
28	B	m	Pneumonia
29	M	m	Injury
30	D	m	"
31	E.	f	"
32	C	f	"
33	S	m	"
34	F	m	Fur ⁿ culosis
35	G	m	Chronic Bronchitis
36	K	m	Rheumatoid Arthritis
37	S	m	Injury
38	B	m	"
39	F	f	"
40	H.	m	"
41	C.	m	"
42	P	f	"
43	H	m	"
44	C	m	"
45	G	m	"
46	B	m	"

CHILDREN UNDER TREATMENT FOR SLIGHT INJURIES OR
FOR AFFECTIONS CONSIDERED NON-TUBERCULOUS.

A. GIVING NO REACTION

1. T.	m	Injury
2. S.	m	"
3. B.	m	"
4. C.	m	"
5. H.	m	"
6. G.	m	"
7. H.	m	"
8. H.	m	"
9. R.	f	"
10 H.	f	"
11 C.	f	"
12 H.	f	"
13. B.	m	"
14 N	m	"
15 R.	m	"
16 L.	m	"
17 B.	m	"
18 F.	f	"
19 P	f	"
20 T	m	"
21. B.	f	Broncho pneumonia
22. W.	m	Pertussis

23	S.	f	Tonsillitis
24	H.	f	Impetigo of head
25	B.	m	"
26	T.	f	"
27	R.	m	Injury
28	G.	m	"
29	C.	f	"
30	H.	m	"

B Giving a positive reaction

31	M.	m.	aet 10	Injury
32	K	m	aet 6	"
33	C.	f	aet 8	"
34	S.	m	aet 5	"

Of the two adults giving a negative reaction, one was suffering from advanced phthisis, the other was a case of sacro-iliac disease, almost certainly tuberculous, though at the time of writing no confirmation of this diagnosis had been made, by operation or otherwise.

Of the four children, not considered tuberculous, who gave a positive reaction, two were anaemic, and of poor nutrition the other two were apparently in good health, but no sign of tuberculosis was found on examination.

The great disadvantage of the reaction in obscure cases is that the lesion is not localised, a positive reaction indicating tuberculosis, but not its site. Again an error may be made by taking a positive reaction to mean that the particular lesion under investigation is tuberculous, while in reality it may be non-tuberculous and the reaction may be due to a tuberculous focus in a different situation which has escaped notice. Such an error was less likely to be made, in the case of an exposed lesion at any rate, when the subcutaneous injection of tuberculin was made, for then the presence or absence of a local, in addition to a general, reaction, was looked for.

The over-violent reaction sometimes obtained may deter some from using the method. But it is noteworthy that in all the cases reported as showing severe after-effects, when the strength of the solution is mentioned, a 1% solution has been used. In children, and possibly also in adults, a solution of $\frac{1}{2}$ % of tuberculin, or even less, is sufficient for a preliminary

application, and would be found to be innocuous in the vast majority of cases, though some regard perhaps should be paid to the contention that, in acute tuberculous conditions, the temporary lowered resistance of the conjunctiva, the result of the reaction, might provide an opportunity for tubercle bacilli in the blood stream to settle there and start a pathological process.

The fact noted by several observers and seen in one of my cases, that a very advanced or moribund case of tuberculosis fails to react, has also been noted by those who have used the subcutaneous injection of tuberculin for diagnostic purposes. It may be due, as some hold, to the low state of vitality of such patients, while others think it due to a condition of "autotuberculinisation".

An interesting point has been brought forward by MacLennan, of Glasgow. He obtained pronounced reactions in cases with a family history of tubercle, but who themselves had clinically no sign of tubercle, and asks, "Is it possible that this reaction not only reveals the presence of an actual lesion, but also a condition of tissue which is susceptible to the development of tubercle?" This question, as he says, can only be answered by prolonged observation of such cases.

Enough evidence has now been given by those who have tried the test to prove that it should be a valuable aid in diagnosing obscure cases, and in determining the cure of recognised lesions which have been under treatment. Its simplicity

places it within the reach of every practitioner. It is probably among his younger patients that the physician will find it of most value. Cases of malnutrition among young children, whose food and surroundings are satisfactory, whose digestive organs are healthy, and in whom no pathological conditions can be found by the usual methods of examination, often puzzle the physician, who may find the problem solved sooner or later by the development of a tuberculous lesion. Among older children, a definite recognisable tuberculous condition is often preceded by such symptoms as anaemia, loss of weight, capricious appetite, change in disposition. In all cases, a positive reaction on the application of Calmette's test should be taken as an indication for the necessity of placing the child under the most hygienic conditions possible, and employing all the well-recognised means of treating tuberculosis. The test could be re-applied at intervals, and it would be interesting to find whether such children, after some months of treatment, failed to give a reaction.

Such a method too, is brought forward opportunely at a time when the medical examination of every school child is an established fact. In the case of children who are found to be obviously in an unsatisfactory state of health, without very definite signs or ⁺ symptoms, the instillation of a $\frac{1}{2}$ per cent solution of tuberculin, a harmless procedure, should be adopted as a routine measure, and a positive reaction taken as proof of susceptibility to, or

of latent infection with, tuberculosis. Special attention should then be given to such children, especially as regards their surroundings at home, their hours of work and sleep, and ^{the} quality of their food. Cod-liver oil, with iron if desirable, should be administered and the weight should be taken at frequent regular intervals. Should they fail to improve, they should be removed to an institution in a suitable situation, where the requisite care and nourishment would be provided.

Time, then, will prove the full utility of the Calmette opthalmo-reaction to tuberculin. At present we are justified in saying that it gives promise of becoming a recognised means of diagnosis of a wide-spread disease, and by giving the inestimable advantage of early diagnosis and therefore early treatment, should save many a life.

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