TUBERCULIN AS A DIAGNOSTIC AND THERAPEUTIC AGENT IN THE TREATMENT OF CONJUNCTIVITIS ECZEMATOSA (PHLYCTENULAR CONJUNCTIVITIS AND KERATITIS)

BASED ON THE STUDY OF FIFTY CASES

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Phlyctenular conjunctivitis and keratitis (conjunctivitis eczematosa, phlyctenulosis) constitute one of the most frequent ocular maladies of childhood. The dominant characteristics of the disease are, first, its chronicity and, second, its tendency to recurrences. Usually it is not reckoned as a serious ocular malady, either in its clinical course or in its sequelae. An extended experience, however, and a careful analysis of the clinical course and sequelae of phlyctenular trouble neither justify this assumption nor satisfy the conscientious scientist with the results obtained by present methods of treatment. When there is taken into account the suffering experienced by many such patients, the prolonged invalidism they must undergo, the unheralded acute attacks of frequent occurrence which they must accept, the inroads on their visual acuity to which each new attack subjects them, the anxieties of parents as to the outcome of the attacks, the educational loss incident to the patient being compelled to remain out of school, the economic loss to the child, to the parents and to the state, the physical retardation and interference with physical and mental development—when all these factors, which are not the unusual, but on the contrary, the common concomitants of a phlyctenular affection, are weighed and measured, the consideration of this disease then assumes a more serious aspect than a mere superficial consideration would lead one to expect. The full force of the hardships, incident to an attack or recurrence of the disease, is better appreciated when one considers that even the mildest attacks require from eight to fourteen days for complete recovery, while in those not unusual cases, where outbreaks rapidly follow each other with slight intermission, the period of invalidism may be prolonged into months or even years. The present recognized treatment of an acute attack of phlyctenular trouble, while far from ideal, might fairly be said to be satisfactory in results, compared to the extremely unsatisfactory results usually obtained by present-day methods in preventing recurrences of the disease. The prevention of these recurrences is the crux of the question, the pressing, insistent problem which confronts the clinician. Each recurrence subjects the patient to additional hazard in the possible limitation of his vision, besides producing and accentuating the manifold ill effects previously alluded to. The largest opportunity and the broadest possibility lie in the prevention of the recurrences. When this phase of the management of such cases has been definitely overcome, the application of the new therapeutic management will necessarily prove equally satisfactory in managing acute attacks of the disease. While the etiology has not been specifically established, phlyctenular disease has, by common consent, been considered to be due to a strumous constitution, a scrofulous diathesis, which, translated into modern scientific lan-

guage, is interpreted as meaning an active or latent tuberculosis. The attacks were observed in connection with some lowering of the general body resistance and a minus resistance of the patient; almost always in association with the "adenoid syndrome"; frequently encountered with tuberculosis of bones and joints and common accompaniments or sequelae of the exanthemata, measles, scarlatina, whooping-cough, or some debilitating illness. In the past, scrofula, or what was termed a "scrofulous diathesis," was held largely accountable for the production of the disease. Modern observers have established what might be termed the "pathologic kinship" existing between scrofula and tuberculosis. This kinship, while perhaps not positively established, has been so well recognized that the Germans speak of those exhibiting the scrofulous diathesis as "candidates for tuberculosis." Investigators have directed their attention especially to tuberculosis as an etiologic factor in the production of the disease.

Mr. Stephenson¹ states: "While nobody asserts that the phlyctenule itself is of tuberculous histologic structure, or that it contains tubercle bacilli, nevertheless it is most ordinarily believed that practically speaking the characteristic lesion occurs only in those who are subjects of tuberculosis, latent or otherwise."

Since Koch's discovery of the specific pathogenic microorganism of tuberculosis and his advocacy of tuberculin as a diagnostic and therapeutic agent, increased impetus has been given the investigation of the subject. The diagnostic measures now available, together with the improved technic for the recognition of tuberculosis, as well as the enlightened public opinion on the subject of tuberculosis, which insures a cooperation on the part of patients hitherto unknown, has been of incalculable advantage in conducting such an investigation.

The announcement of the discovery of tuberculin by Robert Koch created a furore among scientists and laymen. For a considerable period, notwithstanding the earnest protest of its discoverer, it was hailed as the long-looked-for specific in the treatment of tuberculosis. Disappointment in the results obtained by its indiscriminate use soon gave place to ridicule, and ridicule to abuse, and soon both the discoverer and his discovery were enveloped in a maelstrom of unseemly criticism. A small but earnest band of scientific workers, who were neither carried heavenward by the gale of enthusiasm following Koch's announcement, nor precipitated to the bottom of the scientific sea by the wave of criticism which superseded the first enthusiasm, continued to carry on their observations with the new agent. To the dignified insistent attitude of the great master, Koch, during these trying periods, and to the work of his faithful following, suffering humanity and the scientific world is indebted for a revival of the use of tuberculin along the lines first advocated by the great discoverer. "Koch's intention² was to create antitoxins by carefully introducing tubercle toxin into the body of the patient and through introduction of dead, specifically prepared tubercle bacilli in the newer preparation, to produce defensive substances against the morbid agent itself, to 'actively immunize' the patient, as the bacteriologists term it." While probably the therapeutic successes of tuberculin might at this time provoke an animated discussion, the same unsettled opinion does not obtain concerning its diagnostic efficacy. No less an authority

1. Stephenson: Brit. Med. Jour., April 10, 1910.
2. Junius: Ophthalmology, Seattle, 1910, vi, 200.

than Wolff-Eisner³ uses the following emphatic language in discussing its diagnostic value: "Contrary to what has been said concerning its therapeutic value, its diagnostic importance is not to be doubted, and it is hardly an exaggeration to maintain that this discovery stands at the beginning of the diagnostic science of tuberculosis, and our clinical knowledge concerning the distribution of this disease. It seems to have been the mission of tuberculin completely to fill up the gap caused by the loss of the value of the tubercle bacilli for purposes of early diagnosis, and to constitute an extremely fine biologic method by which to discover even the very first stages of tuberculosis."

The various tuberculin tests for the specific diagnosis of tuberculosis are four in number:

1. The cutaneous (von Pirquet).
2. The percutaneous (Moro, Doganoff, Lignières).
3. The conjunctival (Calmette, Wolff-Eisner).
4. The subcutaneous (hypodermic).

An extended consideration of the relative value of these four tests, with their modifications, is not within the scope of this paper. In the selection of a test suitable for the observations which formed the basis of this report, the limitations of and adaptability to the clinical material utilized became a matter of major importance. The hypodermic (subcutaneous) test was not applicable, principally because of the fact that with this ambulatory clinical material it was found impossible to carry out with precision the important details, such as keeping the temperature records, etc., which this test requires. The conjunctival test (Calmette, Wolff-Eisner) was not applicable because it is contra-indicated in any inflammation of the eye or lid; other hazards, such as a prolonged conjunctivitis and ulceration of the cornea, have also been reported from its use. The percutaneous test (Moro, Doganoff, Lignières) is said to be not so dependable as the von Pirquet test, principally because of the variable quality of absorption and the irritability of the skin differing in the different individuals. The cutaneous diagnostic tuberculin test of Pirquet was selected because it lends itself admirably to the investigations of the tuberculous ocular maladies of childhood. Von Pirquet states that the cutaneous test which bears his name is of value chiefly in children. In addition to its special application to suspicious tuberculous ocular diseases of childhood the test commends itself, first, for its comparative freedom from dangers; second, its simplicity of application; third, its freedom from unpleasant and disturbing reactions, focal, constitutional and local; fourth, elimination of prolonged and frequent periods of observation for confirmation; fifth, its reliability of results. Von Pirquet⁴ thus explains the origin of the test:

I had found that in vaccination against small-pox only those persons show local symptoms within twenty-four hours who have formerly been vaccinated. One may therefore conclude, if any early reaction is obtained, that the person has been previously vaccinated. In applying the method of vaccination to tuberculosis, I found that, in the same way, an early reaction at the point of vaccination with Koch's tuberculin proves a previous infection with tuberculosis, and that this cutaneous reaction corresponds to Koch's fever reaction after injection with tuberculin.

The value of the cutaneous reaction as a diagnostic measure has been definitely established not only by extensive clinical observation, but by the post-mortem

findings of von Pirquet. Two hundred of his cases, which had previously undergone the cutaneous test, came to autopsy. In these 200 cases were 109 children with no tuberculosis. In eighty-nine cases tuberculosis was found post mortem, and of these eighty-nine cases, sixty-five had given a positive reaction. No reaction had followed in twenty-four of the eighty-nine. Von Pirquet explained this negative result in the twenty-four, by the statement that no reaction occurs in the terminal stage of the disease, in the last stages of meningitis, in generalized tuberculosis, in miliary tuberculosis, in certain stages of measles, and also that the reaction ceases as the child gets older. The twenty-four negative reactions were explained by their being classed in one or the other of these groups. All the children who had given a negative reaction were found on autopsy to be free from tubercle. Von Pirquet's conclusion⁵ is that "the positive result of the reaction indicates with certainty the presence of active or inactive tuberculous changes." A negative result, when tuberculosis is present, is explained by von Pirquet on the premises previously alluded to. Adults react positively much more frequently than children, on account, it is alleged, of the greater frequency of tuberculosis in the adult. The test is, therefore, more useful in early childhood. Von Pirquet states that a negative result in the adult, after three attempts, proves with certainty that the patient is free from tuberculosis.

In the series which I studied, a careful record was kept of the cases and every essential detail thought to be necessary was carried out faithfully and energetically. The period of observation approximates six months, and the cases studied numbered fifty. A systematic plan of observation was adopted and included:

1. Age of the patient.
2. Type of disease.
3. Duration of disease, with particular reference to frequency of "recurrences," and association with other diseases.
4. Family history, with particular reference to tuberculosis and syphilis.
5. Personal history, with particular reference to tuberculosis and syphilis.
6. General condition of patient.
7. Lymphoid complications, adenoids, enlarged tonsils, adenitis, etc.
8. Results of von Pirquet tests.
9. The local, focal and constitutional effects of the test.
10. Therapeutic administration of tuberculin.
11. The local, focal and constitutional effects of the therapeutic injection.
12. Results of the therapeutic injection on the ocular disease.

In addition to the therapeutic use of tuberculin, the patients were given the usual local ocular treatment of conjunctivitis eczematosa (boric solution, yellow oxid of mercury, calomel, atropin, warm compresses, etc., as indicated) and constitutional measures such as regulation of diet, hygienic conditions, systematic life, exercise, fresh air, tonics, etc., and where complications, such as hypertrophied tonsils, nasal obstructions, adenoids or other diseased conditions existed, these were corrected or treated. The von Pirquet cutaneous reaction test was first applied in all cases, and in the event of a positive reaction ensuing, the therapeutic injections were instituted, after the local reaction and all other untoward developments had subsided completely.

Three negative tests were elicited before the patient was considered free from suspicion of tuberculosis. The

5. Von Pirquet: *Wien. klin. Wchnschr.*, 1907, No. 38.

3. Wolff-Eisner: *The Ophthalmic and Cutaneous Diagnosis of Tuberculosis*, p. 11.

4. Von Pirquet: *Cleveland Med. Jour.*, vii, No. 11.

RESULTS OF THE USE OF TUBERCULIN (DIAGNOSTIC AND THERAPEUTIC) IN OCULAR DISEASE

Case	Age of Patient, Years	Type of Ocular Disease	Duration of Disease	Glandular Complications†	Tub. Family History, Syphilis	Personal Hist., Active Tub. Syphilis	Von Pirquet Positive-Negative	Ocular Reaction, V. Pirquet Test	Temp. with V. Pirquet	Therapeutic Duration of Treatment ‡	Temp. Following First Therapeutic Injection	Result on Ocular Disease of Injection
1	10	Phlyct. Conj. O. D.	Off and on* one year.	Ad. T. Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	March 15....	100	Cured
2	9	Phlyct. Kerat. O. D.	Since 4 years, off and on.*	Ad. T. Gl.....	Father and mother died of consumption.	Negative.....	Negative (3 tests).	Negative...	Negative...			Cured
3	3	Phlyct. Conj. O. D.	2 weeks.....	Ad. T. Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	March 20....	99.6	Improved
4	3	Phlyct. Kerat. O. U.	Since 5 years old, off and on.*	Ad. T. Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	February 27..	99	Cured
5	12	Double Phlyct. Kerat. O. U.	4 months (typhoid)...	Ad. T. Gl.....	Negative.....	Negative.....	Positive...	Slight	Negative...	January 25...	100.2	Marked improvement
6	1	Phlyct. Kerat. O. D.	Since 2 days.....	Ad. T. Gl.....	Negative.....	Negative.....	Negative (3 tests).	Negative...	Negative...			Improved
7	18	Phlyct. Kerat. O. D.	Since 5 years.....	Ad. T. Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	March 1.....	90.4	Improved
8	11	Phlyct. Conj. O. D.	Past 3 years, off and on.*	Ad. T. Gl.....	2 sisters died of pul. tub.	Negative.....	Positive...	Negative...	100.....	No treatment.		Unknown
9	42	Keratitis O. D.....	2 years.....	Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	March 1.....	99	Improved
10	4	Phlyct. Kerat. O. D.	Since 2 years, off and on* (typhoid).	Ad. T. Gl.....	1st cousin died of pul. tub. (paternal).	Negative.....	Positive...	Negative...	Negative...	March 15....	100	Improved
11	22	Phlyct. Conj. O. D.	1 year.....	Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	February 27..	Negative	Cured
12	6	Phlyct. Kerat. O. D.	2 yrs. (scarlet fever).	Ad. T. Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	January	99	Cured
13	9	Phlyct. Kerat. O. U.	1½ years, off and on.*	Ad. T. Gl.....	Negative.....	Negative.....	Negative (3 tests).	Negative...	99 (after third test).			Improved
14	7	Phlyct. Kerat. O. S.	6 months, off and on.*	Ad. T. Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	February 6...	99.2	Cured
15	8	Phlyct. Kerat. O. D.	Since 3 years, off and on* (measles).	Ad. T. Gl.....	Negative.....	Negative.....	Positive...	Slight	Negative...	February 27..	100.2	Improved
16	3	Phlyct. Kerat. O. S.	1 year, off and on.*	Ad. T. Gl.....	Negative.....	Negative.....	1st neg.; 2d pos.	Negative...	Negative...	February 27..	99.2	Cured
17	13	Phlyct. Kerat. O. U.	3 months.....	Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	October	99	Improved
18	56	Phlyct. Kerat. O. D.	6 months (whooping-cough).	Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	October	99.4	Cured
19	6	Phlyct. Kerat. O. D.	6 months.....	Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	October	99	Cured
20	2	Phlyct. Kerat. O. D.	1 year (tonsillitis)...	Ad. T. Gl.....	Negative.....	Negative.....	Negative (3 tests).	Negative...	Negative...			Cured
21	4	Phlyct. Kerat. O. S.	2 months (measles)...	Ad. T. Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	January	99.4	Cured
22	10	Phlyct. Conj. O. U.	2 months.....	Ad. T. Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	February 27..	99	Cured
23	26	Phlyct. Conj. O. D.	2 years.....	Tonsils and adenoids removed; operation for tub. gl. neck.	Mother and father also operated; tub. gl. neck.	Tub. gl. neck was operated.	Positive (strong).	Negative...	Negative...	February 20..	99.3	Cured
24	8	Phlyct. Conj. O. U.	Off and on* for 3 yrs. (bronchitis).	Ad. T. Gl.....	Negative.....	Negative.....	1st neg.; 2d pos.	Negative...	Negative...	March 29....	99	Cured
25	22	Phlyct. Kerat. O. D.	3 months.....	Gl.....	Negative.....	Negative.....	1st neg.; 2d pos.	Negative...	Negative...	March 27....	99.2	Improved
26	31	Phlyct. Kerat. O. D.	2 months.....	Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	March 27....	99.1	Improvement marked
27	41	Phlyct. Kerat. O. D.	6 weeks.....	T. Gl.....	1 son died of pul. tub.	Negative.....	Positive...	Slightly reddened.	100.....	March 1.....	100.2	Improved
28	23	Phlyct. Conj. O. S.	1 year.....	T. Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	January 28...	99.4	Cured
29	4	Phlyct. Conj. O. U.	5 months, off and on.*	Ad. T. Gl.....	Uncle and aunt died of pul. tub. (paternal).	Negative.....	Positive (strong).	Negative...	Negative...	March 31....	100	Cured
30	21	Phlyct. Conj. O. D.	1 month.....	Gl. T.....	Uncle died of tub. (pat.). Another uncle now has tub. pul. (pat.).	Negative.....	Positive (strong).	Other eye showed phlyct.; affected eye reddened.	99.2.....	February 27..	99.2	Cured
31	40	Phlyct. Conj. O. D.	6 months, off and on.*	Gl.....	Negative.....	Negative.....	Positive...	Negative...	99.....	March 1.....	99	Cured
32	2	Phlyct. Conj. O. U.	1 year (scarlet fever).	Ad. T. Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	February 1...	99	Cured
33	40	Phlyct. Conj. O. D.	6 months.....	Gl.....	Negative.....	Negative.....	Positive...	Negative...	Negative...	February 1...	99.3	Cured

34	4	Phlyct. Conj. O. U.	3 years, off and on*	Ad. T. Gl.	Negative.....	Negative.....	Sup. glands of	Negative.....	Positive....	Negative....	November 1..	99.2	Cured
35	18	Phlyct. Kerat. O. D.	2 years, off and on*	Gl. T.	Negative.....	Negative.....	Sup. glands of	Negative.....	Positive....	Negative....	December 4..	99	Cured
36	5	Phlyct. Conj. O. U.	4 years, off and on* (measles)	Ad. T. Gl.	Mother died of pul. tub.	Negative.....	Negative.....	Negative.....	Positive....	Negative....	March 5.....	99.3	Cured
37	6	Phlyct. Conj. O. U.	2 years, off and on* (pneumonia)	Ad. T. Gl.	Negative.....	Negative.....	Sup. glands of neck	Negative.....	Positive....	Negative....	October	99	Improved
38	30	Phlyct. Kerat. O. U.	1 year, off and on*	T. Gl.	1 brother died of pul. tub.	Negative.....	Right lung affected slightly.	Negative.....	Positive (marked).	Negative....	October	100	Cured
39	19	Phlyct. Conj. O. U.	4 years, off and on*	T. Gl.	Negative.....	Negative.....	Negative.....	Negative.....	Positive....	Negative....	October	99.3	Cured
40	30	Phlyct. Conj. O. S.	1 year, off and on*	T. Gl.	Negative.....	Negative.....	Negative.....	Negative.....	Positive....	Negative....	November	99	Cured
41	3	Phlyct. Conj. O. S.	1 year, off and on*	Ad. T. Gl.	Negative.....	Negative.....	Negative.....	Negative.....	Positive....	Negative....	January	99.3	Cured
42	1	Phlyct. Conj. O. U.	2 months.....	Ad. T. Gl.	Negative.....	Negative.....	Negative.....	Negative.....	Positive....	Negative....	January	99	Cured
43	2	Phlyct. Conj. O. D.	6 mos. (chicken-pox).	Ad. T. Gl.	Negative.....	Negative.....	Negative.....	Negative.....	Positive....	Negative....	January	99	Cured
44	6	Phlyct. Conj. O. D.	2 years, off and on*	Ad. T. Gl.	Negative.....	Negative.....	Negative.....	Negative.....	Positive....	Negative....	November ...	99.3	Cured
45	51	Phlyct. Kerat. O. D.	2 years, off and on*	T. Gl.	Negative.....	Negative.....	Abscess of rectum (tub.) not healed; operated 1 year ago.	Negative.....	Positive (marked).	Negative....	November ...	100.1	Improved
46	4	Phlyct. Conj. O. D.	1 year, off and on*	Ad. T. Gl.	Negative.....	Negative.....	Negative.....	Negative.....	Positive....	Negative....	December ...	99.2	Cured
47	2	Phlyct. Conj. O. S.	6 months, off and on.*	Ad. T. Gl.	Negative.....	Negative.....	Negative.....	Negative.....	Positive....	Negative....	January	99	Cured
48	1	Phlyct. Kerat. O. D.	2 months, off and on.*	Ad. T. Gl.	Negative.....	Negative.....	Negative.....	Negative.....	Positive....	Negative....	December ...	99.3	Cured
49	6	Phlyct. Kerat. O. U.	2 years, off and on* (bronchitis)	Ad. T. Gl.	Negative.....	Negative.....	Sup. gland operated	Negative.....	Positive....	Negative....	December ...	100	Cured
50	8	Phlyct. Kerat. O. D.	1 year, off and on*	Ad. T. Gl.	1 brother died of pul. tub. at 19 years.	Negative.....	Negative.....	Negative.....	Positive....	Negative....	November ...	100.2	Improved

* The phrase "off and on" is the usual form of expression used by the patient to describe the "recurrences" or attacks of the disease. The disease which appears in parenthesis beneath the duration periods signifies that the first attack of the phlyctenulosis accompanied or followed the designated disease.

† The letters "Ad" refer to the presence of adenoids as a complication; the letter "T" to enlarged or diseased tonsils as a complication, and the letters "Gl" to the presence of a cervical adenitis.

‡ The dates refer to the time the therapeutic injections were begun.

technic of the von Pirquet test was as follows: The inner side of the forearm, at the point selected, was cleansed with ether, and two drops of Koch's Old Tuberculin, undiluted, were placed on the skin about four inches apart. The special scarifier, previously sterilized, which is supplied with the tuberculin, was applied vertically first to a point midway between the drops and with a circular movement; a very superficial, bloodless scarification was accomplished—this constituted the "control." Next, the scarifier was applied to the first drop and a similar scarification performed; and finally it was applied to the other drop.

A drop of 1 per cent. phenol in glycerin was placed in the "control." A light sterile dressing, secured by adhesive strips was applied, and the patient directed to report within forty-eight hours for inspection.

Following Wolff-Eisner's suggestion the local reactions were divided into three degrees:

1. Distinct reaction.
2. Strong reaction.
3. Very strong reaction.

These terms are self-explanatory, and after limited observation no difficulty is encountered in assigning the reaction to its proper class or degree. A reaction was characterized as positive when, within forty-eight hours, the appearance at the site of the inoculation exhibited a papule surrounded by a hyperemic zone. The size of the papule and hyperemic zone varies, though neither the size nor the intensity is held to be a measure of the extent of the tuberculous process. The reaction of the "control" is, as a rule, very slight and easily differentiated from the inoculation scarifications. The behavior of the reaction, the time of its appearance, the duration of its existence, its intensity and size have each been the subject of much speculation. At the present time, however, no sufficiently positive corroborative conclusions are available covering the theories advanced. The Tuberculin Bacillen Emulsion (B.E.) human type, serial dilutions (Mulford) was used for the therapeutic injections. This product is marketed in six vials, known as Serial Dilutions No. 1 to No. 6, inclusive. Each two minims of Dilution No. 1 contains 1/10,000 milligram; each two minims of the succeeding dilutions is ten times stronger than the preceding solution; for example, two minims of Dilution No. 2 contains 1/1,000 milligram; two minims of Dilution No. 3 contains 1/100 milligram.

The proper administration of tuberculin is emphasized by all observers of large experience. Koch⁶ advises that "the best way of guarding against the misapplication of tuberculin is to use it in cases in which the temperature of the body does not exceed 37 C. (98.6 F.)." Apropos of the faults of administration, Trudeau⁷ writes as follows:

I quite agree with Denys that the principal faults in treatment—faults which may lead to failure and even seriously endanger the patient's chances—are: beginning the treatment with too large amounts; raising the dose too rapidly, or at too short intervals; injecting again before all effects of the reaction, both constitutional and local, have passed away; increasing the dose after a reaction has occurred; neglecting to consider malaise, headache, loss of appetite, and increased cough, as evidence that the limit of the patient's tolerance has been reached and calls for an interval of rest and a reduction of the dose. The physician who disregards, as of no importance, an increase of a minute fraction of a milligram of tuberculin or a rise of a few tenths of a degree of temperature will meet with disappointment and disaster in the use of tuberculin treatment.

6. Koch: Pulmonary Tuberculosis, Philadelphia, 1907.
7. Trudeau: Am. Jour. Med. Sc., cxxxi, 175.

In the question of administration the main factor is the dosage. Each case must be individualized, there being *no average dose*; 1/10,000 milligram, for instance, might be too large a dose for one individual, and one milligram too small a dose for another. In harmony with these observations I followed the plan of beginning, in most cases, with an injection of 2 minims of Bacillen Emulsion, Dilution 1, 1/10,000 milligram; in infants and young children only 1 minim of Dilution 1 was used. If no elevation of temperature occurred about twenty-four hours afterward, or other evidences of reaction, such as marked reaction at the site of injection, nausea, headache, general malaise, etc., appeared, the injection was repeated, usually twice a week, each dose being increased by 2 minims until 20 minims of that dilution was injected; after which Dilution 2 was begun and proceeded with in the same manner. When 20 minims of Dilution 2 was reached, Dilution 3 was taken up and so on, in like manner, the entire series of dilutions were, if possible, exhausted. Any evidence of intolerance, which was exhibited by the development of the symptoms above described, was a signal for reducing the dose, omitting it entirely, or extending the interval of injection; in any event the conduct of the administration was governed entirely by the reaction or toleration exhibited by the patient.

The majority of observers agree that haste in the administration is responsible for much disappointment in the use of tuberculin, and most of them suggest carrying the patient along slowly and cautiously, over a period of at least six months and better still, of one year.

ANALYSIS OF CASES STUDIED

An analysis of the cases studied, shown in the accompanying table, discloses the following facts:

1. *Age of Patients.*—The youngest patient was 1 year old; the oldest, 56; the average age $12\frac{1}{4}$ years, approximately.
2. *Type of Ocular Disease.*—There were twenty-four cases of phlyctenular conjunctivitis (48 per cent.). The right eye was involved in eleven of the twenty-four cases (45.8 per cent.). The left eye was involved in five of the twenty-four cases (20.8 per cent.). Both eyes were involved in eight of the twenty-four cases (33½ per cent.). There were twenty-six cases of phlyctenular keratitis (52 per cent.). The right eye was involved in seventeen of the twenty-six cases (65.3 per cent.). The left eye was involved in three of the twenty-six cases (11.5 per cent.). Both eyes were involved in six of the twenty-six cases (23 per cent.).
3. *Duration of Disease.*—The shortest period, since first attack, was two days. The longest period, since first attack, was five years.
4. *Lymphoid Complications.*—In thirty-two of the cases enlarged or diseased tonsils, adenoids and cervical adenitis were found coexisting (64 per cent.). In nine of the cases cervical adenitis was found alone (18 per cent.). In eight of the cases enlarged or diseased tonsils and cervical adenitis were found (16 per cent.). In one of the cases, the tonsils and cervical glands had been removed.
5. *Tuberculous Family History, Syphilis, etc.*—In ten of the cases a positive family history of tuberculosis was obtained (20 per cent.). In none of the cases was a family history suspicious of syphilis elicited.
6. *Personal History of Active or Latent Tuberculosis, Syphilis, etc.*—In six of the cases a personal history of active or latent tuberculosis was obtained (12 per cent.). In no case were evidences or history of syphilis obtainable.
7. *Von Pirquet Cutaneous Diagnostic Test.*—In forty-six cases a positive cutaneous reaction to the test was obtained (92 per cent.).
8. *Ocular Reaction Accompanying the von Pirquet Test.*—In four cases a varying reaction was obtained following the diagnostic test (8 per cent.).

9. *Temperature Accompanying the von Pirquet Diagnostic Test.*—In five cases an elevation of temperature following the test was observed (10 per cent.).

10. *Therapeutic Duration of Treatment.*—The longest period of treatment was six months; the shortest period about three weeks.

11. *Temperature Following the First Therapeutic Injection.*—In forty-four cases there was a rise in temperature following the first therapeutic injection (88 per cent.). The highest elevation recorded was 100.2 F.; the lowest elevation recorded 99 F.

12. *Result on Ocular Disease of Therapeutic Injection.*—In thirty-two cases the ocular disease had cleared up completely and there had been no further recurrences up to date; these patients were tabulated as "cured" (64 per cent.). In thirteen cases the ocular disease had "improved" but still required treatment (26 per cent.). In two cases the ocular disease had cleared up completely and the diagnostic test proving negative, no therapeutic injections were used (4 per cent.). In two cases the ocular disease had "improved" but still required treatment; a negative von Pirquet being obtained no therapeutic injection was used (4 per cent.). In one case patient did not return for treatment.

In the study of the foregoing cases two main points were to be determined; first, the etiologic relationship existing between tuberculosis and conjunctivitis *eczematosa*; second, the value of tuberculin as a diagnostic and therapeutic agent in the treatment of conjunctivitis *eczematosa*. After a careful consideration, I am convinced that conjunctivitis *eczematosa* should be regarded as a manifestation of constitutional tuberculosis. It is impossible longer to ignore the evidences which point unmistakably to the scientific correctness of this view. A careful study of the symptom-complex of this class of cases exhibit, with every stigma of a tuberculous process accentuated and occurring with startling constancy in each individual case, and these evidences supported and corroborated in unmistakable manner by the investigations of numerous observers leads to but one positive conclusion, and that is that conjunctivitis *eczematosa* is an ocular manifestation of a constitutional tuberculosis, and that tuberculin is the appropriate and especial agent for its proper treatment.

The clinical course of the malady, with its chronicity and tendency to recurrences; its predilection for the poorly nourished and those with a minus resistance; its glandular complications; its response to the tuberculin diagnostic and therapeutic measures, all confirm and emphasize this belief and forces on us a definite line of therapeutics—the proper administration of tuberculin. The preponderance of the rapidly accumulating mass of evidence collected by numerous observers adds weight and undoubtedly will persist in substantiating the correctness of this conclusion. I am convinced, from a careful survey of the investigations of others as well as from a study of my own cases, that conjunctivitis *eczematosa* is an ocular manifestation of constitutional tuberculosis and that its proper management must include not only the usual ocular or local treatment, but more particularly the general or constitutional measures appropriate to the treatment of tuberculosis. At the head of the constitutional agents advised in the treatment of tuberculosis I would unhesitatingly place tuberculin. The favorable results experienced from its use by a large number of observers cannot be denied; the theoretical correctness of the remedy is undoubted and the increasing favor it commands it as a remedial agent of especial value and dependability in the treatment of diseases of tubercular origin.

CONCLUSIONS

The results obtained from the study of the cases forming the basis of this report justify the following conclusions:

1. The tuberculous nature of conjunctivitis eczematosa is established and this opinion is supported by the results obtained in the cases subjected to tuberculin, both diagnostically and therapeutically, and by the majority of the other essential clinical findings.

2. The cutaneous diagnostic tuberculin test of von Pirquet is a dependable method for the recognition of tuberculosis, particularly in children.

3. Tuberculin as a therapeutic agent in the treatment of conjunctivitis eczematosa is an agent of distinct and special value and should be employed faithfully, judiciously and perseveringly in this class of cases.

I wish to express my indebtedness to Dr. J. B. Murphy for suggesting to me the use of tuberculin in this class of cases; to Dr. H. Woodruff, surgeon to the Illinois Charitable Eye and Ear Infirmary, and chief of our clinic, for permission to conduct the major part of these observations; also to Doctors Schenck, Hoffman and Smith, of the house staff of the infirmary, for valuable assistance in carrying on the observations.

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THE EXCITING CAUSES, MEANS OF PREVENTION AND EARLY TREATMENT OF CANCER OF THE UTERUS *

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The cancer problem is unquestionably the most important one before the medical profession to-day. Cancer has always been dreaded by every human being. Owing to the public belief in the incurability of cancer, and the apparent failure, up to the present time, of the surgeon to demonstrate the contrary, there has been a lack of cooperation between public and physician in the endeavor to wipe out this disease. Little progress, therefore, has been made.

There has been a steady increase in the number of cancer victims. According to statistics of the Aetna Life Insurance Co. from 1870 to 1906, of the total deaths in 1870, 426, or 2.6 per cent., were caused by cancer; while in 1906, of 1,514 deaths, 111, or 7.3 per cent., were caused by cancer.

Southgate Leigh reports that there were about 70 per cent. of deaths from cancer to 100,000 people in the United States in 1906. The rate of increase according to Coley since 1868 has been 22 per cent. for males and 44 per cent. for females. In England, in 1909, there were 34,053 deaths from cancer, this being within 2,000 of as many as from tuberculosis.

It is estimated that there are 80,000 cases of cancer in the United States and 40,000 deaths annually from this disease. Cancer causes more deaths in women at the present time than tuberculosis. Of 10,000 women in England and Wales dying during a certain period, 2,209 died of cancer of the uterus. In Japan, according to the report of K. Sato, of 6,430 patients, 33.53 per cent., had cancer of the uterus.

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CAUSES

Coley, Paget, Bilroth, Magraw and many others believe that a large percentage of cancer cases are due to local irritation. It is noted that the working class and those exposed to traumatism are more subject to cancer than the idle or those working indoors. Coley makes the statement, based on over 1,200 personal observations, that "local trauma of any kind from chronic irritation to a single local contusion is not infrequently the direct cause of malignant tumors of all types." Physiologists have been reluctant to acknowledge or to accept injury or irritation as the exciting cause of cancer, but there are enough authentic cases to establish this fact quite well.

Various causes, such as anemia, hard work, uncleanness, etc., prevent healing of raw surfaces in lacerations of the uterus and of ulcers. If such an ulcer existed elsewhere on the body, the patient would not rest until it was cured. These ulcers remain on the cervix for months and years, although much more dangerous than on the outside of the body. E. E. Montgomery says, "Everyone recognizes the fact that a damaged and lacerated cervix is a factor in the development of cancer which is to be heeded, and that such injury is to be treated and cured." The segregation of epithelial cells in the healing of cervical ulcers or lacerations has been offered as an important factor in the cause of cancer of this portion of the uterus.

Dr. Victor Bonney says, that out of 1,876 patients investigated at the Middlesex Hospital Cancer Research Laboratory, 1,796 had been married. Only 9 per cent. had not borne children, and clinically a case in an undoubted virgin was almost unknown. "Every case seemed to be founded on a chronic cervicitis." This belief is shared by many.

The relationship between malignant disease of the cervix, marriage and child-bearing is extremely important from the social standpoint, and in fact is an unjust penalty on the natural function of woman.

PREVENTION

Mayo Robson says, "The arrest or relief of known causes as well as the abolition of discoverable precancerous conditions wherever or however occurring constitute the true preventive treatment."

The most important and efficient means of preventing this disease is to educate the public and the general practitioners. Women should understand that the cervix should be as clean and as free from ulcers, lacerations or abrasions as any other mucous membrane, as a means of preventing local disease. Leukorrhea, menorrhagia and metrorrhagia are abnormal conditions, and medical advice should be obtained at the earliest possible time by women suffering with these complaints. The very location of the uterus makes infection and disease more possible, especially in women who have borne children with a resulting lacerated perineum, gaping vulva and a torn cervix.

When a lacerated perineum is present, it should be repaired so as to make a closed canal below the uterus, thereby preventing infection from the bladder or bowel. The lacerated cervix should be repaired directly after the child is born. This is a condition that has been too long neglected by the profession. In most instances, unless a post-partum hemorrhage or some positive indication of serious uterine trauma calls attention to this organ, the cervix is not inspected after childbirth.

Polypi should be removed as well as fibroids that are degenerating, causing bleeding or enlargement of the