

# SCIENTIFIC SECTION, AMERICAN PHARMACEUTICAL ASSOCIATION

## DIAGNOSTIC REAGENTS AND THEIR USES IN THE DIAGNOSIS OF INFECTIOUS DISEASES.\*

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### ANAPHYLACTIC OR ALLERGIC REACTION.

We now come to a consideration of what are known as the anaphylactic or allergic reactions.

When a foreign protein is introduced into the animal body, the body of a guinea-pig for example, after a definite interval a specific hypersensitiveness of the animal to this protein will appear. After a definite interval a second injection of the same protein may produce violent symptoms of illness and possibly a fatal termination. The first injection of the protein produces no symptoms, but serves to "alter the power of reaction on the part of the body cells by rendering them unusually sensitive or susceptible to the same or to closely related foreign proteins."

This unusual or exaggerated susceptibility of the organism to foreign proteins is generally known as *anaphylaxis* (*ana*, against, and *phylax*, guard, or *phylaxis*, protection), a word introduced by Richet to describe a contrary condition to prophylaxis. However, as we now regard the phenomenon, this word is a misnomer, for as regarded at the present time, this condition of hypersusceptibility or supersensitiveness, is "a distinct benefit and advantage to the organism. In fact, protection against a large class of infections depends on an altered power of reaction, *i.e.*, hypersusceptibility or anaphylaxis" (Anderson).<sup>1</sup>

Von Pirquet proposed the term "allergy," from *ergia* and *allos*, meaning altered energy or altered reaction of the organism, as more appropriate to express this condition than the word "anaphylaxis."

The allergic condition is specific in nature, *i.e.*, while it may be brought about by the introduction of any foreign protein into the body, yet it does not follow that the body has become hypersensitive to any other protein.

Another important point in regard to the allergic condition is that the animal may be in a condition of hypersusceptibility and immunity at the same time. "The two conditions are closely interwoven; the latter is often dependent on the former."<sup>2</sup>

The anaphylactic or allergic diagnostic reactions are therefore due to the altered power of the body to react. "When this power of reaction is increased we say that the body is hypersensitive or in a state of anaphylaxis.

"The tuberculin and mallein reactions are well-known instances of anaphylaxis. These substances are not poisonous when introduced into a healthy individual, but the tuberculous individual is anaphylactic to tuberculin, and an individual suffering with glanders is in a state of hypersusceptibility to mallein.

\* Read before Scientific Section, A. Ph. A., Atlantic City meeting, 1916. Continued from p. 1201, October number.

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<sup>1</sup> Anaphylaxis, by J. F. Anderson and M. J. Rosenau, *Arch. Int. Medicine*, June 15, 1909.

<sup>2</sup> Anderson and Rosenau, *ibid.*

"A clinical instance of anaphylaxis is the hypersusceptibility of some individuals to pollen—hay fever. The best studied instance of experimental anaphylaxis is that produced in the guinea-pig by the injection of a foreign protein; for example, horse serum, egg white, milk, etc."<sup>3</sup>

Schick and von Pirquet studied a large number of infectious diseases, especially smallpox, measles, streptococcic infections, etc. They also studied the reactions to cowpox virus, tuberculin and mallein. They confirmed the observations that the re-injection of a foreign protein following a definite interval after the first injection may give rise to the train of symptoms to which the name "anaphylaxis" has been given; consequently, if an animal manifests this train of symptoms after the injection of the foreign protein, it follows that the animal must have received a previous dose of the same protein.

The diagnostic value of this discovery is apparent when it is considered that an infectious disease is caused by infection with the protein of the microorganism causing the disease; typhoid fever, for example, is caused by the growth and multiplication of the living typhoid bacilli in the body of the infected individual, and, as stated by Vaughan, this infecting microorganism is in fact a living protein, capable of producing anaphylactic phenomena when introduced into the animal body.

Kolmer<sup>4</sup> explains the rationale of these diagnostic reactions as follows:

"If a protein, such as tubercle protein (tuberculin), syphilis protein (luetin), glanders protein (mallein), etc., is concentrated and applied to the skin or mucous membrane in a local area, and if the corresponding antibody or "ferment" is present in the body-fluids, the protein will be digested or split and the liberated protein poison and endotoxin will diffuse into the local tissues and produce a local reaction, characterized chiefly by congestion and oedema. This local reaction, marked by paralysis of the vessel walls with dilatation, is due to the action of the protein poison on smooth muscle, and is analogous to the urticarial or other eruptions accompanying general serum anaphylaxis (serum disease). Since the antibody-protein reaction is highly specific, these tests possess considerable diagnostic value. . . . The same underlying principle governs all. It would appear that these reactions should be obtained in all infections where we can secure and cultivate the causative microparasite. Theoretically, this is true, although practically, the problem is greatly complicated, or indeed impossible, owing to technical difficulties and especially to the fact that the protein antibody for one strain of a particular microparasite may not be identical for all strains."

*Tuberculin Reaction.*—The tuberculin generally employed in the tuberculin tests is that form known as *Old Tuberculin* ("O.T."). It is called "old" to distinguish it from the later preparations suggested by Koch, to whose investigations we are indebted for this important product. It is prepared from pure cultures of the tubercle bacillus of five or six weeks' growth upon 5 percent glycerin bouillon. The culture medium containing the germs is evaporated to one-tenth of its volume and filtered through porcelain to remove the germs. Old Tuberculin contains the soluble products of the tubercle bacilli in a fifty percent glycerin solution.

Relatively large quantities of tuberculin may be injected into healthy persons without causing any symptoms of reaction; but if a very small quantity is injected into a person suffering from tuberculosis, very different symptoms are

<sup>3</sup> Anderson and Rosenau, *ibid.*

<sup>4</sup> John A. Kolmer, *A Practical Text-book of Infection, Immunity and Specific Therapy*, p. 582.

produced. The temperature rises from 1° to 2° F., this rise being accompanied by a feeling of illness amounting sometimes even to nausea and vomiting. Around each localized tuberculous lesion there is produced an area more or less marked with heat and redness. If the resulting congestion is very severe, there may be later a casting off of pieces of necrotic tissues. After the reaction above described has subsided, it is frequently found that a tendency to heal is manifested.

Tuberculin reaction is therefore characterized by three essential features: (1) a constitutional reaction consisting of fever and accompanying general symptoms of malaise; (2) a local reaction at the site of injection varying in intensity from slight tenderness and redness to severe inflammation with adenitis; (3) a focal reaction about the tuberculous lesion. These reactions do not necessarily run parallel.

According to the present theory, this reaction is explained in the following manner: the tubercle bacilli stimulate the body cells to produce digestive enzymes in the nature of an amboceptor which aids in splitting the tubercle protein contained in tuberculin, liberating the protein poison, which produces a general local and focal reaction.

The general reaction is believed to be due to a general effect of the poison on body cells. The local reaction is supposed to be caused by concentration of the poison at the site of administration of the tuberculin, and the focal reaction is presumably due to the fact that body cells about the lesions are more sensitive to the effects of the poison than are other cells, probably because they are most concerned in antibody production.

The tuberculin reactions are highly specific, if they are not of as much value in diagnosis as was at first supposed, owing to the fact that by far the greater proportion of supposedly well people react to the test because tuberculosis is an exceedingly common infection, from which a large majority of infected persons spontaneously recover.

False positive reactions may be observed in leprosy, a disease caused by a bacillus which bears close morphological and bacteriological resemblance to the tubercle bacillus. Massive doses of tuberculin injected subcutaneously may produce a toxic fever in debilitated, non-tubercular individuals. However, when a positive reaction occurs in a person supposed to be in health, it is safe to assume it is due either to a small hidden tuberculous lesion, or to a healed tuberculous lesion.

In the focal stage of tuberculosis, the patient may not react at all. This is to be explained by assuming that the tissues have become so thoroughly saturated with tuberculin produced by the infected area that they are incapable of responding to further artificial stimulation. In the first stages of infection no reaction may occur, because sufficient antibody has not been formed to produce reaction, and other cases given in the text-books explain false negative reaction which cannot here be considered for lack of space.

*Subcutaneous Method.*—Various methods have been proposed for making the tuberculin test. The following is the method of application used by Roth-Schulz,<sup>5</sup> who used tuberculin at the Beelitz Sanatorium from 1902 to 1905, in over 1000 cases. "The temperature and pulse-rate of the patient to be investigated are carefully noted for from four to seven days, after which, in the event of these being normal or only very slightly elevated, an initial hypodermic injection is

<sup>5</sup> Francine's Pulmonary Tuberculosis, Second Ed., 1907; *Beitrag zur klin. der Tuberkulose*, 1906, No. 12.

given of 0.5 mg. Old Tuberculin.<sup>6</sup> If no reaction follows this in from three to four days, the same dose is usually repeated, particularly if any symptoms indicative of a mild reaction have occurred. If the temperature shows any irregularities, a longer period is allowed to elapse and the same repeated a third time. Usually, however, in the absence of reaction, the second dose is increased to 1.25 mg. This amount may be repeated after the lapse of two or three days without reaction, or the dose increased to 2.5 mg. This maximum dose may again be repeated. The importance of repeating the same dose is emphasized, as often a merely suggestive reaction after the first administration may be followed by severe symptoms after the second dose.

"A rise in temperature of 1° F. (0.5° C.) above the previous maximum is considered positive, but great importance is attached to the development of general and local phenomena. Even in the event of only a slight rise in temperature, the development of râles where they were previously absent, or the occurrence of general symptoms, is considered positive."

*Contra-indications for the Subcutaneous Use of Tuberculin.*—Lerbourne<sup>7</sup> gives as contra-indications for the use of tuberculin the following: "Recent hemorrhages, nephritis, and tuberculosis of the kidney. Ill-nourished individuals and convalescents from acute infections."

Numerous attempts have been made to ascribe some prognostic value to the tuberculin reaction. M. Petit considers the reaction to indicate a virulent tuberculosis. Moeller, Kyserling and Turban state that "a violent reaction indicates a recent infection, and vice versa."

The local reactions to tuberculin depend upon the fact that the cells of a tuberculous individual are highly sensitized to tuberculin and when in contact with an extremely minute amount are stimulated to an enormous production of antibodies. This is characterized by hyperemia and inflammatory changes at the point of application.

*The Cutaneous Reaction.*—Von Pirquet<sup>8</sup> pointed out the fact that upon scarifying the skin of a tuberculous subject and applying a solution of tuberculin, there appears an area varying from a local hyperemia to an intensely inflammatory reaction. Many times the reaction is characterized by the appearance of a small papule, the disappearance of which is followed by a brownish pigmentation. The reaction is not attended with fever, malaise or any other general symptoms.

The method of carrying out the von Pirquet reaction as outlined by Lawrason Brown<sup>9</sup> is as follows: "The cutaneous method consists in putting a drop of diluted Old Tuberculin, preferably 25 percent, upon the skin, and then with a lancet, quill or von Pirquet's scratcher (*Schaber*), a slight abrasion of the skin, under the drop of tuberculin, is made. Only the most superficial layers of the epithelium need be removed, as it is only necessary to open the superficial lymph channels, and it is unnecessary and even undesirable to draw blood. The technic to be employed is practically the same as that used in vaccination against small-pox, and the dangers of secondary infection are exceedingly slight. At a dis-

<sup>6</sup> Equivalent to 10 min. of Serial Dilution No. 3.

<sup>7</sup> "Le Diag. de la Tuberculose." M. Villairt et L. Tixier. *Revue de la Tuberculose*, June, 1908, p. 239.

<sup>8</sup> *Weiner medicinische Wochenschrift*, 1907, Nos. 27 and 28.

<sup>9</sup> *Boston Medical and Surgical Journal*, July 23, 1908.

tance of about one inch a control<sup>10</sup> abrasion should be made under a drop of 50 percent glycerin and 0.1 percent phenol in physiological saline solution. Care should be exercised not to carry tuberculin on the instrument to the control, and where large numbers of patients are vaccinated, a platinum-iridium instrument that can be heated has been advised."

The value of the von Pirquet reaction is variously estimated. It is an extremely delicate reaction and on that account often reacts with individuals who appear to be practically free from tuberculosis. However, as pointed out by Hamberger,<sup>11</sup> it is quite difficult to find an adult free from tuberculosis, which explains the great frequency of von Pirquet's reaction in adults. Its greatest value is in the diagnosis of tuberculosis in children.

Jules Lemaire<sup>12</sup> distinguishes three grades of the von Pirquet reaction as follows:

"Feeble reaction: Hyperemic zone 4 to 6 mm. in diameter, in the centre of which is a papule; the skin slightly swollen and hard.

"Medium reaction: Hyperemic zone 6 to 12 mm. in diameter; numerous papules very prominent. The skin is quite œdematous throughout the area. The redness persists for several hours.

"Strong reaction: All of the foregoing conditions are very much exaggerated. The area of reaction gives a very resistant sensation to touch and the zone of hyperemia extends from 2 to 3 cm. If the sub-adjacent œdematous area is pronounced, it gives an appearance of urticaria. Occasionally at the points of scarification there is an exudate of serous fluid."

*Ophthalmic-Reaction.*—Wolff-Eisner,<sup>13</sup> and simultaneously, Calmette,<sup>14</sup> found that the instillation of a dilute solution of tuberculin into the eye of a tuberculous patient was followed in a few hours by a local reaction, characterized by a congestion of the palpebral conjunctiva and caruncle, with a more or less abundant serofibrinous exudate which tended to accumulate in the inferior cul-de-sac.

Calmette's modification of Wolff-Eisner's method consists in the use of a precipitated and purified tuberculin, as the glycerin present in Old Tuberculin is of itself an irritant. The ophthalmic test has but a limited field of use and is not employed to the same extent as formerly. It was dropped in human practice on account of laceration to the eye, but is still employed more or less for diagnosis of tuberculosis in cattle.

*The Moro Reaction.*—The following diagnostic reaction as described by Moro,<sup>15</sup> its originator, has attracted considerable attention:

"A tuberculin ointment is prepared by a combination of equal parts of Old Tuberculin and anhydrous lanoline. The lanoline base is selected because with this material it is possible to prepare a very concentrated ointment. The mixture is made at a temperature of from 20° to 30° C.

"Ten grams of ointment is sufficient for 100 tests. The point of application is over the skin of the abdomen or over the breast near the mammæ. The ointment is energetically rubbed on the skin for one-half to one minute. The area of the

<sup>10</sup> The Mulford von Pirquet test outfit includes control tubes containing concentrated glycerin bouillon. This is superior to 50 percent glycerin for control, since it contains all the constituents of Old Tuberculin except the products of the tubercle bacilli.

<sup>11</sup> *Muenchener medicinische Wochenschrift*, 1908, No. 23.

<sup>12</sup> *Beitrage zur klin. der Tuberkulose*, Bd. ix, Heft 1.

<sup>13</sup> *Beitrage zur klin. der Tuberkulose*, Bd. ix, Heft 1.

<sup>14</sup> *C. R. Academy of Science*, cxliv, 1907.

<sup>15</sup> *Muenchener medicinische Wochenschrift*, Feb., 1908, No. 5.

part treated is about two inches. The positive effect is noted by the eruption of a granular or a papular efflorescence at the point of application."

Moro divides the reaction into three groups:

"*First*.—A weak reaction. At the point of application there appear, after twenty-four to forty-eight hours, seldom later, single distinctly red nodules, from two to ten in number, of a diameter of 1 to 2 mm. This efflorescence disappears after a few days and at no time has caused any itching or other irritation.

"*Second*.—The medium reaction. At the point of application there appear in the first twenty-four hours numerous (one hundred or more) miliary or larger red nodules, about 3 mm. in diameter. The skin surrounding the eruption is intensely red. The reaction is confined to the point of application, and is accompanied by considerable itching. This remains several days and then disappears.

"*Third*.—The strong reaction. At the point of application there appear within a few hours one hundred or more large nodules or papules, upon an inflammatory base. The dermatitis associated with it is accompanied by intense itching. Many of the eruptions form an exudate and often reach a size of from  $\frac{1}{8}$  to  $\frac{1}{4}$  inch in diameter.

"The reaction is not only confined to the point of application, but extends into the surrounding area. After a few days the papular efflorescence dries up, leaving a brownish pigmentation of the skin which remains for several weeks. General symptoms, namely, rise of temperature, etc., do not accompany the reaction.

"The strong reaction occurs seldom. In thirty-seven positive reactions, we only observed it three times, two of these cases being scrofulous and one caries of the bone. The weak reaction was observed twenty-five times, and the medium reaction nine times in the thirty-seven cases.

"The most distinct reaction is observed in scrofulous conditions and tuberculosis of the bones. Weaker reactions occur most often in cases of tuberculosis of the lungs.

"An important factor in determining the stage of the reaction is without doubt the sensibility of the skin."

Moro gives a table showing the value of the percutaneous reaction with the cutaneous vaccination of von Pirquet. In sixteen cases of undoubted tuberculosis twelve were positive with the percutaneous reaction and fourteen positive with von Pirquet's reaction. In twelve cases of scrofulous conditions, six reacted positive to the percutaneous reaction and six positive to the von Pirquet reaction. In twenty cases of probable tuberculosis, twelve reacted positive with the percutaneous and twelve reacted positive with the von Pirquet reaction. Of twenty-five cases of non-tubercular patients, three reacted positive with the von Pirquet. Of sixty-eight cases, twenty-one of children of suspected tuberculosis reacted and four children with manifest tuberculosis.

"The ointment reaction is strongly specific. All cases that gave a tuberculin ointment reaction also gave the cutaneous tuberculin reaction described by von Pirquet. A positive ointment reaction without a positive von Pirquet reaction I have at no time observed. The ointment reaction is absolutely harmless. The occurrence of itching at the point of application occurs only relatively seldom."

Dr. Med. Emil von Emmerich<sup>16</sup> gives a very interesting report concerning the value of the cutaneous and percutaneous (Moro) tuberculin reaction. He does not consider von Pirquet's reaction to be of value in adults. His conclusions are

<sup>16</sup> *Muenchener medicinische Wochenschrift*, 1908, p. 20.

as follows: "By the Moro reaction fewer reactions result in clinically tuberculosis-free individuals than by the use of the von Pirquet reaction. Out of sixty cases clinically free from tuberculosis, forty-four reacted positive with the von Pirquet reaction, and only nineteen with the Moro reaction. The Moro reaction is much easier carried out than the cutaneous reaction and is absolutely harmless."

Regarding the conjunctival and cutaneous tests, Dr. Edward R. Baldwin<sup>17</sup> states:

"1. The conjunctival tuberculin test performed with weak solutions by a single instillation has some value in confirming the presence of tuberculosis in the early stages.

"2. It has little value in confirmation when the symptoms of tuberculosis are only suspicions.

"3. Its value in distinguishing 'active latent' from healed tuberculosis in apparently healthy persons has not yet been determined.

"4. Repetition of the test in the same eye has no advantage over the cutaneous and subcutaneous tests in the percentage of reactions produced, and may be misleading and dangerous.

"5. Repetition in the other eye by the author's method offers so little advantage that it cannot be recommended.

"6. The conjunctival reaction is unreliable for prognosis.

"7. Used with the proper precautions, danger to the eye is slight, and need not preclude the test when other methods are inapplicable, as, for example, when fever is present. It should be restricted to adults, since the cutaneous test has been found equally valuable for children and is harmless.

"8. The subcutaneous test by the simultaneous use of dilute and strong tuberculin offers a method of detecting at once or excluding tuberculous infection with no danger of inconvenience. Further experience is needed to show the value of this method.

"9. The subcutaneous test should be restricted to those cases where a reaction at the site of disease is desired, or where the other tests result negatively."

The cutaneous test "as introduced by von Pirquet, is the most suitable method for general use, and is absolutely harmless. It is the only test required for children, because a positive result is more significant of a recent infection and occurs less often in apparent health under the age of twelve. Other methods may be needed in adults to confirm the results of a cutaneous test, but it can be applied as a preliminary method in all cases with advantage."<sup>18</sup>

*Tuberculin Intradermal Test.*—The following tests are used intradermally; that is, by injecting the material employed for testing *between* the layers of the skin, and *not* subcutaneously. The injections may be made by an ordinary hypodermic syringe provided with a small, very sharp needle, or by the so-called "Mulford Hypodermic Syringe." As the latter is a new instrument and may be employed for intradermic tests of various kinds herein described, the illustrations given apply equally to the intradermal tuberculin test, the luetin test for the diagnosis of syphilis, and the Schick test.

The object of applying the bacterial protein *between the layers of the skin*

<sup>17</sup> "Conclusions from 1087 Conjunctival Tuberculin Tests by a Uniform Method," reprinted from the *Transactions of the Sixth International Congress on Tuberculosis*, Sept. 28–Oct. 5, 1908.

<sup>18</sup> "General Principles of Tuberculin Diagnosis and Treatment," reprinted from the *Journal of the American Medical Association*, January 22, 1910.

is to cause a local disturbance which can easily and accurately be observed. If the bacterial protein is injected under the skin, it is taken into the blood stream and distributed through the body, so that when split up by any specific ferments or antibodies that may be present, or that may be formed by tissue cells, the reaction in most cases is so slight as to be scarcely or not at all observable and of no diagnostic value. It is important, therefore, in carrying out the intradermic tests, that a small amount of material be injected *between* the layers of the skin, so that when it is attacked by antibodies formed by the cells, or already present, the toxic substance is liberated and causes a *local* inflammation. If the patient is not suffering from the infectious disease corresponding with the test material, or has not been immunized against such disease, no reaction will occur except that due to traumatism, which disappears within twenty-four hours.

The suggestion that tuberculin be used intradermally for diagnostic purposes was first made by Mendel<sup>19</sup> (1908), who believed that infiltration of the skin with tuberculin would be a delicate and satisfactory means of determining tuberculin hypersensitiveness. This method has been developed and extensively used in man by Mantoux.<sup>20</sup> Mantoux employs 1 to 10,000 dilution of tuberculin, the amount injected containing 0.005 mg. of Old Tuberculin.

The intradermic tuberculin test is a very delicate one, and good results can be obtained only by exercising great caution in the care of syringes, etc.

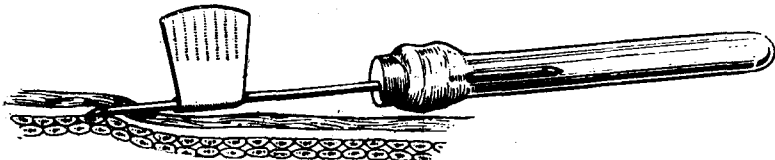


FIG. 1.—Showing method of inserting needle between layers of skin.

The positive reaction consists of infiltration and hyperemia about the site of injection, resembling that following the von Pirquet cutaneous test. It appears in six to eight hours, reaches a maximum in twenty-four to twenty-eight hours, and usually disappears in six to ten days.

Mantoux and Lemaire<sup>21</sup> report the results of intradermic tests in 300 apparently healthy children. Among children from a tubercular environment in the first year of life, 16 percent reacted; in the second and third, 51 percent; from the fourth to the sixth, 65 percent; from the seventh to the fourteenth, 84 percent. Among children not so intimately exposed to the disease in the first year of life, 11 percent reacted; in the second and third year, 12 percent; from the fourth to the sixth year, 45 percent; from the seventh to the fifteenth, 66 percent. Although the number of cases is small, the figures indicate that the test is more delicate than the cutaneous test. Mantoux and Roux<sup>22</sup> performed the intradermic test and the cutaneous test simultaneously upon fifty-two children and found the former far more delicate than the latter.

*The Luetin Reaction for the Diagnosis of Syphilis.*—For this test an extract of the killed culture of the *Treponema pallidum* (*Spirochæta pallida*) is employed. This extract is called *Luetin*. The killing of the spirochetæ for this

<sup>19</sup> *Med. Klin.*, 1908, iv, 402.

<sup>20</sup> *Muench. Med. Woch.*, 1908, No. 40.

<sup>21</sup> *Semaine Med.*, 1909, xxix, 371.

<sup>22</sup> Mantoux and Roux: *Cit. Muenchen. Med. Wochenschr.*, 1908, iv.



purpose is effected by heating to 60° C.; 0.5 percent trikresol is added as a preservative. The preparation is carefully tested to insure sterility, and is then placed in sterile ampuls or capillary syringes.

This test is made by selecting a site on the skin of the arm, cleansing and sterilizing, and then injecting the luetin into the skin as superficially as possible. The injection should be made *between* the layers of the skin, and *not* under the skin. If properly done, a small, pale swelling is produced which subsides in from 10 to 15 minutes. The following phenomena indicate the various types of positive reactions.

(a) The *papular type* consists of a large raised papule, reddish in color and usually 7 to 10 mm. ( $\frac{1}{4}$  to  $\frac{1}{3}$  inch) in diameter, which makes its appearance in 24 to 48 hours. The papule may be surrounded by a diffused redness and show marked telangiectasis. The size of the papule and the induration may increase slowly during the following 4 to 5 days, after which it begins to recede and the color gradually becomes dark brownish-red. The induration gradually disappears within two weeks.

(b) The *pustular type* resembles the papular type until about the fourth or

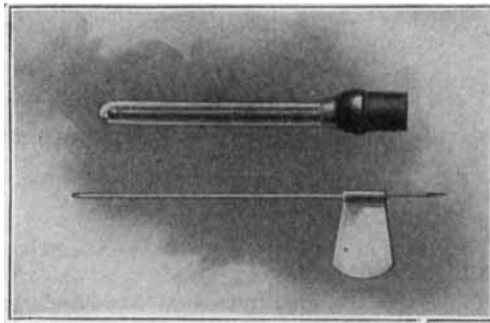


FIG. 2.—The Mulford intradermic syringe. The luetin is contained in the sealed capillary tube and thus protected from contamination. The needle is especially designed for intradermic injection. The longer end acts as a plunger when inserted through the rubber cap, expelling the luetin from the tube through the needle and between the layers of the skin.

fifth day, when, instead of beginning to recede, the inflammatory process increases in intensity, the surface of the papule becomes oedematous, with the formation of multiple miliary vesicles and a central softening of the papule. Within the following 24 hours the papule is converted into a vesicle filled with serum, which later becomes purulent. The pustule soon ruptures and becomes covered with a crust that falls off within a few days, leaving a small induration which is converted into a cicatrix after healing.

(c) In the *torpid type* the site of injection fades to an almost invisible point within 3 to 4 days, so that it may erroneously be considered a negative reaction. After ten days, or even longer, the spot suddenly begins to enlarge and goes through the same stages as seen in the pustular type.

Noguchi<sup>23</sup> reports the results of the cutaneous reaction in 642 cases, comprising 315 syphilitics, 77 parasyphilitics and 250 controls.

In cases of primary and secondary syphilis which had had either insuffi-

<sup>23</sup> "Serum Diagnosis of Syphilis and Luetin Reaction," by Hideyo Noguchi, M.D., M.Sc., Associate Member of the Rockefeller Institute for Medical Research, pub. by J. B. Lippincott Company, Phila. (Third ed.), 1912.

cient treatment or no treatment at all, the reaction was negative except in a few instances in which the positive reaction was of the indurated papular type.

Most of the syphilitics in the secondary stage who had been treated with mercury followed by salvarsan, and who remained without symptoms for some months thereafter, gave strong positive reactions. In cases of tertiary and late hereditary syphilis, there is usually an intense positive reaction. It is in these cases that the luetin test is one of the greatest value. By this means it is possible to diagnose the disease in its diverse and obscure manifestations—a feature of great importance when it is desired to ascertain whether or not internal lesions are syphilitic. In this stage of the disease the Wassermann reaction is frequently negative, especially when patients have received recent treatment.

In parasyphilitic cases the reactions were so variable that no definite decision could be made regarding their diagnostic value.

Dr. Noguchi and others have reported on numerous cases of tuberculosis,

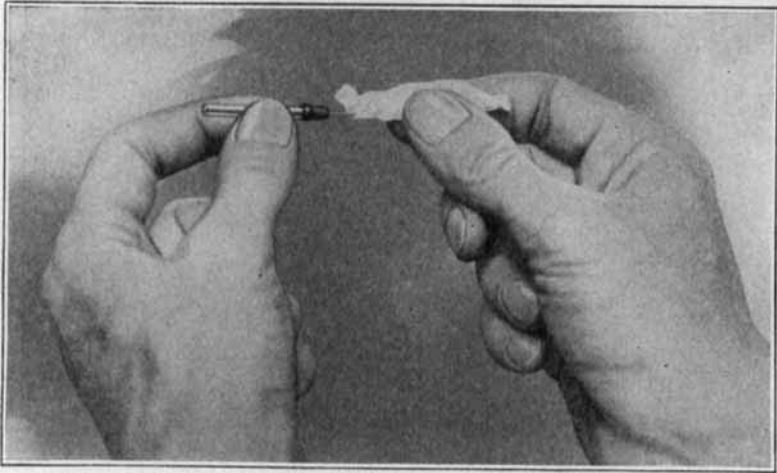


FIG. 3.—The needle is sterilized and protected by a sterile wrapping and envelope. The red end of the wrapper should be torn off without touching the part of the needle thus exposed. Place a drop of an antiseptic on the rubber cap. The end of the needle exposed by removal of the portion of wrapper is then pushed through the rubber cap until the end of the needle inside the tube is visible just below the rubber cap. The remainder of the paper is then carefully removed without contaminating the needle.

leprosy, pneumonia, typhoid fever and various diseases other than syphilis in which the test was applied, and in none of these did a positive reaction occur.

Based upon observations by various investigators since Noguchi, the value of the luetin test may be summarized as follows:

The luetin reaction is specific for syphilis.

It occurs most constantly and intensely during the tertiary and latent stages.

It is usually absent or very mild in the primary or secondary stages, although in these stages it may become positive after energetic treatment.

In infants with congenital syphilis it is less marked than in adults with congenital syphilis.

If a patient who gives a positive luetin reaction is tested again after a month's interval, the reaction takes the same form. If the test is made at shorter intervals than a month, the reactions appear somewhat quicker, showing a shortening of the incubation period. When an injection of luetin is made within one week after the positive reaction, only a mild reaction takes place, occurring within 24 hours and quickly fading away.

According to Noguchi and others, the luetin reaction is little affected by the usual intermittent mercurial treatment, with the exception, as previously stated, that in primary and secondary syphilis, the reaction may become more positive under the mercurial or salvarsan treatment. Theoretically, the test should become negative only when all of the spirochetes of the body of the patient have been killed. In practice, however, the negative luetin reaction should never be relied upon as an evidence that the patient is cured.

Noguchi states: "The absence of the clinical and serological signs of syphilis

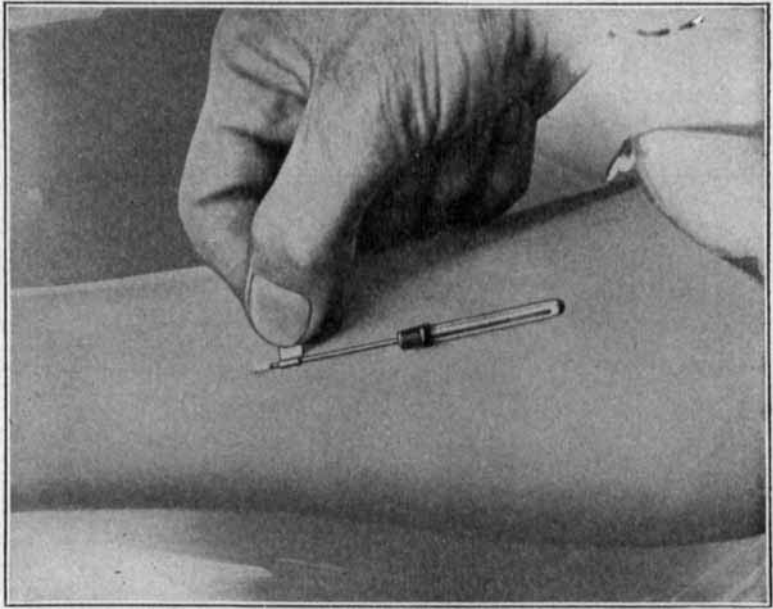


FIG. 4.—The skin at the site selected for making the test is sterilized. Holding the needle by the finger rest, it is carefully inserted between the layers of the skin.

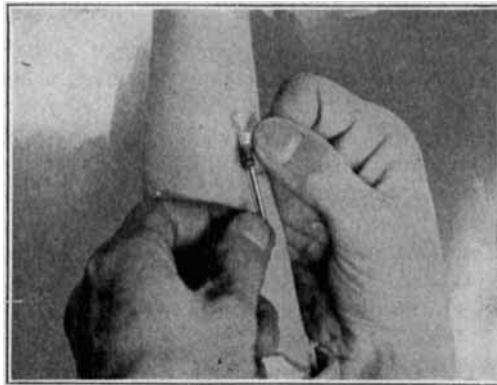


FIG. 5.—The capillary tube is pushed up on the needle and the luetin forced between the layers of the skin, forming a small swelling. Each syringe contains sufficient for one test. Caution should be exercised in making the injection to see that the material is really going between the layers of the skin and not under the skin. If no raising of the skin is visible after the tube has been pushed up part of the way on the needle, it is evidence that the needle has been inserted through the skin and it should be withdrawn and inserted more superficially. The needle should be held as nearly parallel with the skin as possible.

of a period of one year is certainly an encouraging aspect; but, considering the possibility of these signs being absent in some latent cases, one has a right to hesitate in pronouncing these cases cured. It is in this connection that the Luetin reaction may become a great aid in settling this important question. As already stated, the luetin reaction alone cannot decide the point, but combined with other means of diagnosis, it is bound to throw some light on this problem."

*The Schick Test.*—For Determining Susceptibility to Diphtheria and the Need of Prophylactic Injections of Antitoxin. The Schick test offers a simple and accurate method of separating persons likely to be attacked by diphtheria from non-susceptible individuals. A minute quantity of diphtheria toxin<sup>24</sup> is injected intradermally, and if antitoxin is absent or present in such small amounts as to be insufficient for protection of the individual, a positive reaction appears in twenty-four to forty-eight hours. It is evidenced by a circumscribed area of

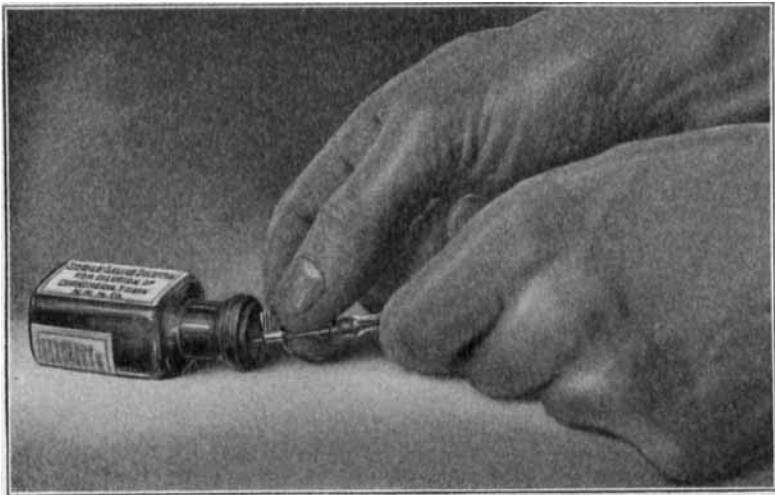


FIG. 6.—The needle is then thrust through the rubber cap on the 20 c.c. vial of sterile saline solution which serves as a diluting fluid and the tube pushed up on the needle, expelling the concentrated toxin from the tube into the salt solution. The tube is moved gently up and down on the needle to draw in and expel the salt solution and wash out all the toxin. The vial is then thoroughly shaken and, finally, the syringe is drawn full of the now diluted toxin and is ready for making the test.

redness and infiltration from 1 to 2 cm. in diameter. This remains from seven to ten days, and on its disappearance leaves a superficial scaling and browning pigmentation. The amount of toxin advised by Schick is 1-50 of the minimum lethal dose for guinea-pigs. When this amount of toxin is injected intradermally, it is, according to Schick, necessary that at least 1-30 of a unit of antitoxin to each c.c. of blood be present in order to prevent the appearance of a reaction. Schick considers this amount of antitoxin in the blood sufficient to protect against diphtheria.

Park, Zingher and Serota<sup>25</sup> report that in the scarlet fever pavilion of the Willard Parker Hospital, 700 patients were tested by the Schick method, and of these 400 (70 percent) gave negative reactions. Only those who reacted positively were immunized. Although 25 percent of the negatively reacting patients

<sup>24</sup> After dilution, the toxin should be used within twenty-four hours, as it deteriorates rapidly.

<sup>25</sup> Archives of Pediatrics, July, 1914, p. 481.

became carriers of the diphtheria bacillus during their stay, no case of diphtheria developed among them. The remaining 300 patients were immunized with toxin-antitoxin mixtures, and among those who reacted sufficiently to this method, 42 developed diphtheria, although a great majority of the cases were a mild type. The greatest number of individuals susceptible to diphtheria, as shown by the Schick test, in these 700 cases, were between the ages of one and four years.

These results coincide with tables furnished by Schick, which show positive reactions in 7 percent of the newborn, 43 percent during the first year of life, 63

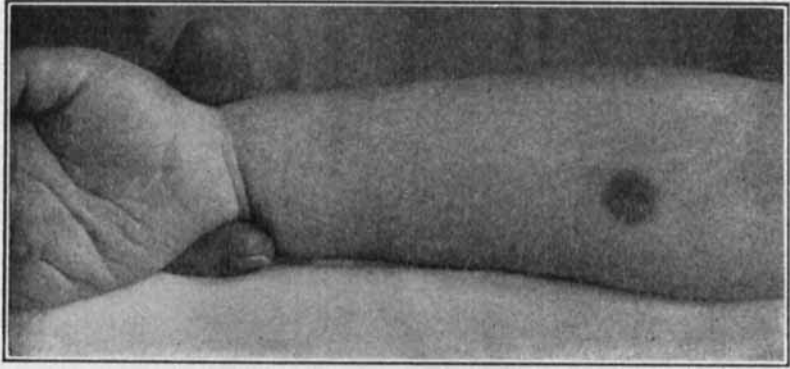


FIG. 7.—Positive Schick reaction. (From Park, Zingher and Serota, *Arch. Pediatrics*, July, 1914.)

percent between 2 and 5 years, and 50 percent between 5 and 15 years. In adults, the positive reactions were not more than 10-percent.

According to these authors, it is important to distinguish between a true reaction and a pseudo-reaction—the latter sometimes occurring in older children and adults who have a large amount of antitoxin in their blood. A pseudo-reaction can be distinguished by its early appearance, greater infiltration, being less sharply circumscribed, and disappearing in twenty-four to forty-eight hours. It leaves a faintly pigmented area which does not show superficial scaling.

#### CACAO DISEASE FOUGHT IN ECUADOR.

The cacao growers in Ecuador are deeply concerned over the appearance of a contagious disease which, when it attacks the fruit, completely destroys it. According to Señor Augusto N. Martinez, director of the agricultural experiment station at Ambato, the malady is caused by a fungus included in the *Peronosporaceæ*, and bearing the name *Phytophthora cactorum*, of Cohn and Lebert, formerly known as *P. omnivora*, Bary, and *Peronospora fagi* of Hartigs, or a closely allied species.

The growth develops in the moisture on the outside of the pod, entering it through some aperture doubtless due to some insect, and destroys it. The development of the fungus requires considerable moisture and a comparatively low temperature. It is checked at 30° C., and dies in four hours at 40° C.

As solutions of copper salts have failed to destroy the fungus, better cultural methods have been recommended.—Consul General Frederic W. Goding in *Commerce Reports*.