

dwelt on the fact that potassium iodid has not the slightest claim to be considered an agency of any value whatsoever to combat the activities of the pale spirochetes that I hesitate to revert to it again. And were it not for the fact that I encounter practically no cases of syphilis of the nervous system which have not been treated with potassium iodid, I should not again speak of it.

There is no more justification for considering potassium iodid an antisyphilitic agency, in the strict sense of the term, than there is for considering it an anti-tuberculous agency.

In order that the forms of nervous syphilis that are not susceptible to cure by any treatment shall be prevented, it is necessary that these patients be treated during the course of the disease when the syphilosis is susceptible to treatment. That is, during the state of sensitization of the structures of the nervous system by the spirochetes.

There are two substances that kill the pale spirochetes—arsenic and mercury. Their administration encompasses the cure of syphilis. To administer successfully is an art. Some acquire this art early and easily, some never acquire it. It can never be acquired save by experience.

A NOTE ON THE OCCURRENCE OF PSEUDOREACTIONS ON THE SKIN

WITH SPECIAL REFERENCE TO THE SCHICK
TOXIN TEST *

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While the value of the Schick toxin test for immunity in diphtheria has been fairly well established and accepted as reliable by numerous investigators who have agreed on the essentials, the practical value of the test is somewhat impaired by the occurrence of atypical and so-called pseudoreactions which may occur in susceptible and immune persons alike and which, even in the hands of experienced persons, are difficult or indeed impossible of differentiation from the true toxin reaction, especially in the first twenty-four hours after the injection has been made.

In conducting this test, especially on a large scale, a number of persons will present at the site of injection within twenty-four hours a small area of redness and infiltration which may be interpreted as a positive toxin reaction, whereas it may be demonstrated that they will react in a similar manner to an injection of the same amount of bouillon alone, and furthermore show that they are immune to diphtheria toxin by reason of the presence of more than one-thirtieth unit of antitoxin per cubic centimeter of serum. We are confident that we have misinterpreted such false reactions for true toxin reactions, and believe that others may have done likewise; certain technical factors, the study of all reactions for a period of at least forty-eight hours and longer, and probably the use of a control fluid are important or necessary to conduct and interpret the Schick toxin test properly, and under these conditions

the percentage of persons immune to diphtheria will be found to be somewhat larger than commonly believed.

As far as we are aware, Park, Zingher and Serota¹ were the first to draw attention to pseudoreactions, ascribing them mainly to probable local anaphylactic reactions of a general character, due to the presence of protein substances in the bouillon used in cultivating the diphtheria bacillus and preparing the toxin, and describing them as of earlier development, more infiltrative, less sharply circumscribed, faintly or not at all pigmented and never followed by true scaling. Schick,² however, has not drawn particular attention to them. Owing to the difficulty we frequently experienced in detecting and differentiating these reactions from the true toxin reactions, we regarded all reactions evidently not traumatic as positive,³ and unless a control bouillon is injected at the same time, we believe this is generally unavoidable especially if it is necessary to read the reactions at the end of twenty-four hours, as in the case of an outbreak of diphtheria when it is desired to immunize exposed nonimmune persons as soon as possible. Weaver and Maher,⁴ Graef and Ginsberg⁵ and Moody⁶ have observed pseudoreactions as described by Park and his associates; Bundesen⁷ does not mention them in his paper.

According to our studies in this subject, we would ascribe these false or pseudoreactions to the following:

1. To trauma due to the injection of a fluid containing tricresol into the epidermis of persons whose *skins are for some reason unduly sensitive*. We believe that this is the most important factor, and to obviate it as far as possible requires that the injection be of as small a bulk of fluid as practicable and made with a fine needle after proper cleansing of the skin.

2. To local anaphylactic reactions of a general protein character as described by Park. We subscribe to this view principally because of certain experimental data at hand indicating that general proteolysins are present in the body fluids which may digest such general protein substances as are contained in broth, or the protein substances may serve to saturate the unsaturated fatty acids (antitrypsin) of the blood serum followed by a release of tryptic activity and digestion of the patient's own serum protein (Jobling and Petersen and Bronfenbrenner), with the formation of proteotoxins capable of producing local reactions of redness and edema, rather than on the basis that we are capable of positively distinguishing these reactions clinically at the end of twenty-four hours from the true toxin reaction. These experimental studies were made in collaboration with Dr. Philip F. Williams in a study of Abderhalden's "protective ferments" and the nature of his pregnancy reaction, and will be described in other communications.

In order to study the pseudoreaction in relation to the toxin reaction, we have made intradermic injections.

1. Park, W. H., Zingher, A., and Serota, H. M.: The Schick Reaction and Its Practical Applications, *Arch. Pediat.*, 1914, xxxi, 481.
2. Schick, B.: Die diphtherietoxin Hautreaktion des Menschen als Vorprobe der prophylaktischen Diphtherieerumsinjection, *München. med. Wchnschr.*, 1913, lx, 2608.
3. Kolmer, J. A., and Moshage, E. L.: The Schick Toxin Reaction for Immunity in Diphtheria, *Am. Jour. Dis. Child.*, March, 1915, p. 189.
4. Weaver, G. H., and Maher, L. K.: The Diagnostic Value of Intracutaneous Injection of Diphtheria Toxin (Schick Reaction), *Jour. Infect. Dis.*, 1915, xvi, 342.
5. Graef, C., and Ginsberg, G.: Some Observations of the Schick Test, *THE JOURNAL A. M. A.*, April 10, 1915, p. 1205.
6. Moody, E. E.: The Intradermic Diphtheria Toxin Test, *THE JOURNAL A. M. A.*, April 10, 1915, p. 1206.
7. Bundesen, H. N.: Schick Reaction, *THE JOURNAL A. M. A.*, April 10, 1915, p. 1203.

* From the Laboratory of the Philadelphia Hospital for Contagious Diseases.

tions of various dilutions of bouillon in doses varying in bulk from 0.05 to 0.2 c.c. while conducting a series of Schick tests. In a number of tests, normal salt solution containing 0.25 per cent. tricresol was also used as a control fluid.

Two toxins were used: the first with a minimal lethal dose of about 0.0085 c.c., obtained from Dr. A. P. Hitchens of the Mulford Biological Laboratories, and the second with a minimal lethal dose of about 0.01 c.c., obtained from Dr. Ayer of the Bureau of Health Laboratory. Both toxins were used in one-fiftieth the minimal lethal dose and so diluted with sterile normal salt solution containing 0.25 per cent. tricresol that this amount of toxin was contained in 0.05, 0.1 and 0.2 c.c. of fluid. With a toxin having a minimal lethal dose of 0.01 c.c., the injection of one-fiftieth of this amount equaled the injection of 0.0002 c.c. of the undiluted toxin bouillon. By means of injecting the three different amounts all containing the same dose of toxin, we were able to study the influence of the amount injected on the question of traumatic reactions.

Sterile bouillons made in the same manner as that used in preparing the toxins were kindly furnished us by the laboratories named above. Both were sugar-free veal bouillons (*Bacillus coli* fermented) with the addition of 0.2 per cent. dextrose and an end-reaction of about +0.85 in one (Mulford) and +1.2 and 0.1 per cent. dextrose in the second (City Laboratory). To both bouillons was added 0.4 per cent. tricresol in order to liken them in this respect to the toxin bouillons, for, in the preparation of toxin, this amount of tricresol is added by routine to kill the culture prior to filtration. Both bouillons were then diluted with sterile normal salt solution in such manner that the dose injected contained 0.0002, 0.002 and 0.02 c.c. bouillon, equal to the amount of toxin bouillon injected (0.0002 c.c.) and 10 and 100 times this amount, respectively. These three dilutions were used in three different doses, namely, 0.05, 0.1 and 0.2 c.c., and in this manner we were able to study the influence of the amount of bouillon protein and amount of fluid injected in relation to pseudoreactions.

In addition to these, we have tested the irritant action following the intradermic injection of 0.2 c.c. of sterile normal salt solution containing 0.25 per cent. tricresol as a control fluid when conducting toxin tests.

In all instances, readings were made at the end of twenty-four and forty-eight hours, and in the majority of cases, observations were made over a period of several days.

The majority of the Schick tests with controls were conducted with persons in the measles, scarlet fever and diphtheria wards of the Philadelphia Hospital for Contagious Diseases; a number were among patients in the isolation and children's wards of the Philadelphia General Hospital. Scarlet fever and diphtheria patients had received antitoxin prior to the tests, while of the patients ill with measles, only those giving true toxin reactions were immunized with antitoxin.

The results of this study may be summarized as follows:

A. The great majority of pseudoreactions appear to be due not so much to the injury of the epidermis by the needle and the fluid injected as to a peculiar hypersensitiveness of the skin in certain individuals.

B. This hypersensitiveness was found most evident among persons in the various stages of scarlet fever.

It was also more apparent among children who had measles than among normal children. Of 103 persons in the scarlet fever wards receiving an intradermic injection of the same amount of bouillon (0.0002 c.c.) as contained in the toxin, about 60 per cent. showed a false reaction at the end of eighteen hours, while at the end of forty-eight hours, the reaction persisted in but 7 per cent., and in seventy-two hours in but 2 per cent., the latter showing a pseudoreaction corresponding to the description given by Park and his associates. Therefore, in conducting the Schick test, an interval of forty-eight hours should be allowed before reading the results whenever time permits.

C. These reactions were characterized by areas of erythema which were rather poorly colored and defined, irregular in outline, measuring roughly from 0.3 by 0.3 cm., to as much as 1.5 by 2.0 cm., and accompanied by some edema at the site of injection. The majority of these reactions, however, did not measure more than 0.5 cm. in any diameter, and were located just about the site of the injection. We are not able safely to differentiate these false reactions from true toxin reactions at the end of eighteen or twenty-four hours; after this time the great majority of traumatic or false reactions subsided, while a few persisted for a day or so longer, whereas the true toxin reactions persisted for several days and left a pigmented area and well-defined scaling of the epidermis.

A number of the scarlet fever patients had received 2,500 units of antitoxin within ten days prior to the time these tests were made, and it was particularly apparent that some persons showed no reaction at all with either toxin or control fluid, while of those showing a reaction, the size, general appearance and duration of each reaction were almost identical with the toxin and bouillon control injections.

This peculiar skin hypersensitiveness among persons who have scarlet fever or who had just recovered from the infection is shown by the large percentage (46 per cent.) of similar reactions following the intradermic injection of 0.05 c.c. of sterile normal salt solution containing 0.25 per cent. tricresol. After twenty-four hours these reactions rapidly and entirely disappeared. Among normal persons this injection was practically always without effect.

D. Among persons with diphtheria, normal children and children with such diseases as vaginitis, digestive disturbances and the like as ordinarily found in children's hospitals, false pseudoreactions were found in about 7 to 8 per cent. at the end of twenty-four hours, and practically all of these reactions subsided and disappeared within forty-eight hours.

E. The amount of fluid injected bears a slight relation to the question of traumatic reaction in that the injection of 0.2 c.c. of fluid produced about 8 per cent. more reactions than when 0.05 c.c. were injected, both doses containing the same amounts of protein constituents and preservatives. What little difference exists in the percentage of false reactions following the injection of 0.1 c.c. and 0.05 c.c. of fluid is in favor of the latter, and when a proper syringe is at hand, it is better to inject the smaller dose (0.05 c.c.).

F. The amount of bouillon constituents injected was found to have less influence on the question of false reactions within the limits of this investigation than the total amount of fluid injected. For example, the percentage of false reactions following the injection of 0.02 c.c. bouillon was about 4 per cent., whereas with

0.0002 c.c., about 2.6 per cent., both doses being contained in the same amount of fluid, namely, 0.05 c.c. On the whole, therefore, it is better to use a highly potent toxin for the Schick test, one that requires high dilution, in order to reduce the quantity of protein and other constituents to a minimum. Schick used a toxin having a minimal lethal dose of 0.005 c.c., and injected one-fiftieth this amount so diluted as to be contained in 0.1 c.c.; this amount of toxin, therefore, corresponded to 0.1 c.c. of a 1:1,000 dilution.

CONCLUSIONS

1. In conducting the Schick toxin test for immunity to diphtheria, it would appear advisable to use as highly potent toxin as possible and to inject one-fiftieth or one-fortieth the minimal lethal dose so diluted with normal salt solution as to be contained in 0.05 or 0.1 c.c. The percentage of tricoresol present should not be more than 0.25 per cent. In this manner the protein constituents of the toxin bouillon are reduced to a minimum owing to high dilution, and trauma of the epidermis is correspondingly reduced.

2. When time permits, it is better to read the reactions after forty-eight than after twenty-four hours, although in the presence of exposure to diphtheria it may be advisable and necessary to inspect the reactions and immunize nonimmune or positively reacting persons at the end of twenty-four hours.

3. The use of a control fluid composed of a bouillon diluted 1:10 or 1:100 and injected in the same amount as the toxin will aid in the detection of skin hypersensitiveness and pseudoreactions, and this is especially indicated when persons suffering with scarlet fever and measles are being tested. Otherwise the use of the control fluid is not absolutely necessary, although in the routine employment of the Schick test without a control injection, a small percentage of persons may be regarded after twenty-four hours as reacting positively on account of mistaking a pseudoreaction for a true toxin reaction.

In our experience, very small areas of erythema about the site of injection measuring, for example, about 2 or 3 millimeters in the largest diameter, may safely be regarded as purely traumatic reactions; but with larger areas we have been generally unable to differentiate at the end of twenty-four hours between the true and the false reaction, and for the purpose of caution usually regard them as toxin reactions and administer antitoxin.

Even under these conditions the use of the Schick test will obviate the necessity of giving antitoxin to about 40 or 50 per cent. of persons, and it is probably better in the presence of exposure to diphtheria to err on the side of giving antitoxin to an immune person than to withhold it from a nonimmune.

Second and Luzerne Streets.

Conservatism and Real Progress.—I will, however, venture to remind you that real progress does not consist in wiping out the past. That idea comes from Germany. A prudent veneration for the best of what has been left to us is ever a wholesome sign of the minds that are to guide the future. Well-gathered experience will always count for much in practical medicine. Knowledge that comes too quickly and too copiously has often to be recast and modified, and the elders do good service sometimes by calling a halt for meditation, for open minds and level heads. Moderation is one of the few things that last long in this world.—Sir Dyce Duckworth, *Lancet*, London, Nov. 28, 1914.

TUBERCULIN IN SURGICAL TUBERCULOSIS

WITH SPECIAL REFERENCE TO THE USE OF SENSITIZED BACILLARY EMULSION *

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Tuberculin, according to the generally accepted conception of its therapeutic status, is a valuable adjunct in the treatment of certain types of surgical tuberculosis. In many cases the results are too striking to be denied, the lesion showing improvement after the first or second dose, and rapidly progressing to a complete and final cure.

Sahli¹ is quoted as saying:

All localized tuberculosis is suitable for tuberculin treatment provided the patient's system is not already overloaded with tuberculin.

According to this view, tuberculin treatment is indicated in every case of localized tuberculosis in a patient not too seriously ill to react to injection. Philip states the case more conservatively, and says in substance:

In proportion as the disease is localized, the hope of successful treatment by tuberculin is increased. In a case of early tuberculous infection, when the process is limited to the lymphatic system, or in a case where, with further advance, the disease is still for the most part localized and the systemic disturbance relatively slight, the well regulated use of tuberculin affects the patient favorably and in many cases leads to a cure.

However, that there is a potency for harm in tuberculin is recognized even by its strongest advocates. Its administration requires careful selection of the cases, close observation of the patients and appropriate regulation of the dose. Because of these requirements, it has been argued that tuberculin has no place in the dispensary treatment of surgical tuberculosis, but should be confined to patients under hospital or sanatorium supervision. That even under the best conditions the treatment is often unsatisfactory is evidenced by the fact that the search for new preparations apparently never ceases.

Encouraged by the good reports following the use of sensitized gonococci and streptococci in infections due to the corresponding organisms, I have investigated the action of the sensitized bacillary emulsion of tubercle bacilli (S. B. E.) in cases of tuberculosis under dispensary control. The results are given subject to such handicaps as are always present in the dispensary treatment of surgical tuberculosis. These patients are difficult to control, and in many cases travel from clinic to clinic in search of relief, never staying long enough in any one dispensary to permit of satisfactory observation or treatment. Moreover, they are anxious to return to work, and stop attendance after improvement has begun, only to return later after a relapse has rendered further treatment necessary. For this reason, the cases chosen have been those in which operation was not indicated, or cases in which a tuberculous sinus persisted after one or more attempts at radical cure. It is in these cases that tuberculin treatment meets its greatest indication.

* From the Department of Surgery of Vanderbilt Clinic, College of Physicians and Surgeons, New York.
1. The Present Status of Tuberculin, Miscellany, *THE JOURNAL A. M. A.*, March 14, 1914, p. 873.