SHOULD THE SCHICK TEST BE ABANDONED?*

WILFRED H. KELLOGG, M.D.

Director Bureau of Communicable Diseases, California State Board of Health, Berkeley, Calif.

THE PROCEDURE of Schick testing preliminary to immunization has been so generally recommended and has become so well established that the two are indissolubly linked in the minds of most of us, and it would almost seem that the idea was sometimes harbored that the Schick test was a necessary part of the process of immunization; but in this paper evidence is presented to support the contention that the Schick test for diphtheria susceptibility should be abandoned absolutely, not only in private but also in public health practice.

An extensive and accumulating experience in the Schick testing of large groups of persons, both children and adults, and the retesting of them after toxin-antitoxin immunization, has brought to light a number of sources of error that constitute a danger both from a public health standpoint and as regards the welfare of the individuals concerned. These drawbacks to the use of the test have not been generally recognized, although some of them have been noted by others; but there has been voiced no appreciation of the seriousness of the situation nor any question as to the advisability of modifying the practice regarding the use of the test in connection with the immunization of children against diphtheria.

ERRORS DUE TO PROTEIN SENSITIVENESS

The occurrence of reactions due to sensitiveness to some of the proteins of the toxin mixture is a great and hitherto unappreciated source of error in the interpretation of the readings of the Schick test. It is the general understanding that protein reactions can be easily distinguished by using a heated control to compare with the test reaction, the theory being that the protein reaction reaches its height in 24 to 48 hours, while the Schick is not fully developed until 96 hours have passed. Furthermore, the protein reaction is expected to fade quickly, being about gone when the positive Schick is at its height. This is in the main correct, but there are so many variations such as rapidly developing and quickly fading toxin reactions and slow fading protein reactions, that many errors result; more than would ever have been thought possible or known, had it not been for the large series of Schick tests controlled by the guinea pig method that have been observed.

The difference in color between the true toxin reaction and the protein reaction is frequently not demonstrable. Protein reactions oftentimes have a bright red color instead of the purplish tinge which is expected to help in distinguishing between the two, and sometimes even these characteristics seem to be slightly reversed. The error from protein reactions is usually that of interpreting them as a positive Schick which is on the safe side, but the opposite sometimes happens. The percentage of error in reading reactions in those who are protein sensitive is, in the hands of even the most experienced, frequently as high as 50 per cent.

In one group of 94 persons in the Eldridge State Home tested by both methods and selected because of the oc-

* Read before the 54th Annual Meeting of the California Medical Association, Yosemite Valley, Calif., May 19, 1925.

currence of pseudo reactions, there were 22 that could not be decided between positive and negative by the Schick test. Of these, 4, or 18 per cent, were found to be unprotected and 18, or 82 per cent, were found to be immune by the Kellogg[1] test. One case reported as having a negative pseudo reaction, was found to have no antitoxin and two that were read as positives were found to be protected. This makes an error of 27 per cent in the readings of this group. A group of university students gave an error of 10 out of 46. In a group of 66 persons tested in the California School for the Deaf and Blind 14 were read as combined positives. Of the 14, 7 were found to be actually unprotected while 7 had antitoxin in protective amount. The error was 50 per cent but on the safe side.

One child in Willits and one in Ukiah developed diphtheria, one in January, 1924, and the other in November, 1924. Both of these children had been regarded as showing negative pseudo reactions in October, 1923, and consequently they had not been given the toxin-antitoxin with the others. The error in this case was unavoidable as the Schick test readings were made by two highly competent persons, epidemiologists in the State Department of Health with a record of thousands of tests to their credit. A boy in the Sonoma State Home, tested by us in April, 1923, was regarded as having a negative pseudo reaction; no toxin-antitoxin was given, and in December, 1924, he developed diphtheria.

POSSIBILITY OF LOCAL IMMUNITY

When a straight Schick negative occurs in a suspectible person and the toxin used is known to be potent, about the only explanation possible is that there are differences of reactivity in different skin areas of the same individual, accounted for possibly by some form of local immunity. It is difficult, of course, to accept this explanation in the case of toxin susceptibility but apparently it must be considered.

In several tests that have recently been made in which two separate Schick tests were placed on the same arm, one above and one below the elbow, it was noted that there was frequently a marked difference in the degree of reaction in the two locations. In one case, the protein reaction was noticeable on the lower arm and absolutely nothing was observed on the upper arm. In two cases very severe positive reactions occurred on the lower arm and very slight reactions on the upper arm. In another case, this arrangement was reversed, no reaction appearing on the lower arm, but a definite positive Schick developing on the upper arm. All of these variations occurred in a group of 11 persons.

Evidently, the series of duplicate tests in the same individual made at the same time, reported by Park,[2] in which 2 per cent showed one positive and one negative reaction, is to be classed in the same group as to cause. This means 2 per cent of false negative reports, a serious matter for the persons concerned. In the Ukiah group, a child of 8 years gave a straight negative Schick in October, 1923, and accordingly was not immunized. In February, 1924, she developed diphtheria. An inmate of the Sonoma State Home at Eldridge was Schick tested by us in April, 1923, the result being a straight negative. In 1924, he was reported as having diphtheria, although in this particular case there was no bacteriological confirmation. Dr. Sippy of Stockton has reported a case that gave a negative Schick test in May, 1924, following toxin-antitoxin immunization, and which developed diphtheria in June, 1924.

These examples of false negative Schick tests are not to be explained by lack of skill and experience on the part of the operators. Leaving ourselves out of consideration, if the skill of Park and his associates is not a guarantee against false negatives due, so far as we know, to the manner of making the injection or possibly to variation in local skin reactivity, it follows that this must occur every-

where, and it will be a safe assumption that Park's figures of 2 per cent represent the absolute minimum of such errors.

Further examples of false negative Schicks are found in those persons giving a positive Schick reaction after a previous negative one. Two children in the Ukiah schools who were found negative in October, 1923, were found positive in October, 1924. One or the other must have been wrong, unless an immune person can lose his protection. The latter possibility has evidently not seemed likely in the minds of investigators generally. The well-known steady increase of immunes as age increases, is distinctly against the idea, because there is evidently a natural and inherited tendency toward the development of antitoxin immunity, and, furthermore, no instances of loss of protection have been observed when it has once been demonstrated by the Kellogg test.

LATE APPEARANCE OF REACTION

Sometimes the Schick reaction does not commence to show itself until after the usual time set for the final inspection. On the basis of 4 days for the full development of the reaction, it is the custom to look at the arms for the last time on the 4th day. That this may result in a false negative report is shown by the experience in a Lodi school where 2 children were examined and recorded as negative on the 4th day, and the reactions began to appear late on that same day and were confirmed as positive at a later visit to this school.

DETERIORATED TOXIN

Probably the greatest single obstacle to accuracy in the Schick test is the tremendous instability of diphtheria toxin. Under the influence of light, air, lapse of time, dilution and other less well understood influences, the toxic portion of the substance is steadily going over into toxoid, which is inert so far as the skin test is concerned. Of course, this process is slow in a well "ripened" toxin, but it frequently happens that a sudden drop in strength occurs. The smaller the bulk of the toxin, the more likely are these changes to occur.

In the usual commercial Schick test package, toxin for 50 tests (1 minimal lethal dose) is placed in one bottle and its bulk is so small that it can hardly be perceived at all. Sterile salt solution is furnished to dilute it to the proper strength. The several causes of deterioration already mentioned are favored by this method of packing, which is unavoidable when small amounts are supplied. The deterioration of the toxin is a particularly serious matter for the physician applying only a few tests at a time, for he has no check whatever against false negatives from this cause, and is likely to consider his patients immune, when a fresh and active product would show them susceptible. This must happen frequently, as laboratory tests by the standard lethal test method, of many different packages of different makes, have shown an astonishingly high percentage of inert material to be on the market. These toxins were all right when they left the manufacturers; they passed the Hygienic Laboratory test and were well within the expiration date on the package; but many did not withstand the deteriorating influences afterward. Fifty-one samples were tested from 14 lots supplied by 6 manufacturers. Twenty-nine samples were shown to be not potent, and only 3 lots had no non-potent samples.

It may be supposed that physicians will be on their guard for poor toxin and will suspect the material if too many negative results are being obtained. Theoretically, this may be so, but not practically. The practitioner will not think of this, and he is told nothing of it by the manufacturer in the literature accompanying the package. On the other hand, those who are doing large numbers of tests might be expected to be on the watch for such trouble, but experience shows that they also frequently overlook it.

In a small town, 380 children were given the Schick test by physicians who were well trained but not experienced in this work. They used toxin put up by one of the most reliable biological houses and were not at all disturbed when they obtained only 25 per cent of positive reactions. This same group of physicians tested 300 children in another school, and we assisted the health officer in reading the reactions. The only positives obtained were in the two lower grades, all of the children above these grades giving negative reactions. Different lots of toxin had been used in the upper and lower grades, so this showed conclusively that the toxin used in the upper grades had deteriorated. On learning that only 25 per cent of positive reactions had been obtained in the other town, we offered to retest them, and when this was done the result was 75 per cent of positives.

FALSE NEGATIVES AFTER IMMUNIZATION

It seems likely that there is some influence tending to make the Schick test unreliable in those recently immunized with toxin-antitoxin. Experience with a group in the California School for the Deaf and Blind, seems to show that false negative reactions may be obtained in those immunized and that the percentage of successful results of this procedure may not be so high as we have believed. The results obtained in this group are disturbing to our confidence in the Schick test, for we obtained an unusual number of false negatives with a toxin which later passed the animal potency test satisfactorily. Incidentally, this shows a disappointing failure to obtain immunity with toxin-antitoxin and shows that there is probably also a tendency for this product to deteriorate suddenly as does toxin.

DISCUSSION

The practice of immunizing children without regard to their immune status has everything in its favor, and it has no disadvantages. In discontinuing the Schick test, we are abandoning a procedure that, even if not subject to the weaknesses already mentioned, is only of academic interest so far as the age group requiring immunization is concerned.

The time to immunize children is between the first and second years, not after they have entered school and have already run the gauntlet of exposure to infection. Our figures show that in California, about 60 per cent of the cases of diphtheria are under 9 years of age, while only about 25 per cent of the immunizations have been in this group. The younger children are practically all susceptible, fully 80 per cent in most localities. Added to this almost universal need of immunization, we have the fact that the toxin-antitoxin in the form now used gives no disturbing reactions in children of this age. There is, therefore, no reason at all why any chance, no matter how small, should be taken of permitting any child to escape immunization by reason of a false belief in its immunity. Out of every large group of children subjected to one test or treatment, there will always be a certain number who never appear for the second. Therefore, if this first interview with the physician is for an injection of toxin-antitoxin instead of for a Schick test, the entire group will have received at least one of the series of immunizing injections.

In small groups where it is desired to know whether or not an individual is immune, and this may apply with some reason to adults who are sometimes subject to rather severe protein reactions, the laboratory test which is previously referred to may be used. This test requires only a small quantity of blood, from ½ to 1 c.c., and it may be taken from a vein with a fine needle or by puncturing the ear lobe as for the Widal test.

As to the testing of immunized children later for the determination of immunity, the experience with the Blind School group previously referred to, shows the futility of using the Schick test for this purpose. It does not matter whether the

finding of such a high percentage of actually unprotected persons among those giving negative Schicks following toxin-antitoxin immunization is to be explained as a curious exception to the normal behavior of the Schick reaction due to the toxin-antitoxin, or whether it is an example of the possibility of error in primary Schick tests. In either case it is a failure of the Schick test. The testing for susceptibility after immunization will have to be reserved, therefore, to the comparatively small number of individuals in whom there is more than the usual interest in the outcome of the procedure. These will be tested by guinea pig inoculation according to the method referred to as the only accurate method available. For public health purposes, the control of the disease will be just as effective if the small percentage who do not gain an immunity with one series of toxin-antitoxin injections remain susceptible.

SUMMARY AND CONCLUSIONS

1. Observations are recorded showing that the Schick test is subject to errors in its application, which more than offset the value of the information derived from its use. The causes of the errors are:
   a. Unavoidable error in technique of the injection, possibly also including variation of skin reactivity in different areas.
   b. Unavoidable errors in the interpretation of pseudo reactions.
   c. Deterioration of toxin against which there is no control when a few tests only are being made.
   d. Lack of sufficient experience in the use of the test which multiplies all possible sources of error.

2. A high percentage of false negative Schick tests has been found in persons following immunization, the information as to their true status having been determined by laboratory test using the Kellogg method.

3. The Schick test is of academic interest only and should be abandoned completely for the following reasons:
   a. It is subject to a sufficient percentage of false negative readings to result in the failure of protection of children who otherwise would have been protected.
   b. Knowledge of the immune status of children is not required, as most of those in the age group most concerned are susceptible, while immunization of the balance is open to no objection.
   c. General immunization of children without further attention to whether or not immunity has been attained, will result in complete public health control of diphtheria.

4. For determining the immune status of individuals and small groups, where this information is specially desired, the laboratory test of the author is convenient and accurate.

REFERENCES

1. Kellogg, W. H. The Intra-cutaneous Guinea Pig Test (Kellogg), etc. *Jour. A. M. A.*, 80:748–750 (Mar. 17), 1923.
2. Park. *Jour. A. M. A.*, 79:1584 (Nov. 4), 1922.