

# HYPOSENSITIVITY TO FOREIGN PROTEIN IN SCHIZOPHRENIC PATIENTS

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## INTRODUCTION

A generalized hyporeactivity of various functions in schizophrenia has been observed and studied at the research service of the Worcester State Hospital. The results of these studies have recently been summarized by Angyal, Freeman, and Hoskins.<sup>1</sup> They found that the schizophrenic patient is hyporeactive in at least three major fields: general metabolism, functions of the vegetative nervous system, and functions of the central nervous system.

In the present investigation, the attempt is made to determine whether a hyporeactivity is present in the functions of immunity also, with the reaction to repeated intracutaneous injections of a protein used as an indicator.

It is well established that practically everyone can be sensitized to a foreign protein by repeated intracutaneous injections of it (Dujardin and Decamps,<sup>2</sup> Jones and Mote,<sup>3</sup> Mote and Jones,<sup>4</sup> Simon and Rackemann<sup>5</sup>). The degree of variation in sensitivity from person to person has been only partially determined. Since considerable interindividual variation may be expected, only distinctly large differences can form the basis for valid distinction between groups.

## PROCEDURE

The development of hypersensitivity to guinea pig serum, injected intracutaneously at weekly intervals, was studied in a group of 12 schizophrenic male patients and in a control group of 12 unselected male subjects. Guinea pig serum was used because, as Simon and Rackemann<sup>5</sup> have pointed out, it rarely acts as an antigen in ordinary life. This serum was buffered with normal saline solution; a dilution of 1:100 was used in all experiments. One-tenth of 1 per cent of phenol was added as a preservative, and a new lot of serum was prepared only every third or fourth week instead of every week as was done by Simon and Rackemann.<sup>5</sup> One-tenth of 1 cc. of this diluted serum was injected intracutaneously in the flexor surface of the forearm. The successive weekly injec-

tions were alternated between the arms, the first injection in the left, the second in the right, and so on. Both patients and normal subjects had injections from the same lot of serum on the same day and at the same time.

The first evidence of sensitization to a foreign protein as detected in the skin is a delayed erythematous reaction which appears at the site of injection in about 24 hours. After this delayed type of hypersensitivity has developed, a few additional injections result in the development of an immediate reaction, with a residual delayed reaction. This immediate reaction, which appears about 10 or 15 minutes after the injection, consists of a raised wheal at the site of injection and a surrounding erythematous flare. With a few further injections, the wheal and the surrounding flare become more prominent, and there is little or no trace of the injection after 24 hours. After the immediate reaction has reached its maximum of development, it probably begins to decrease in intensity with still further injections (Phillips<sup>6</sup>).

The cutaneous reactions to these injections were measured with a millimeter scale. If the reacting areas of the skin were elliptical, instead of being circular, both their long and short axes were measured. Observations and measurements were made after each injection at the following times: the first after 10 to 15 minutes, the second after one hour, the third after nine hours, and the fourth after 24 hours. In this way, the maximum reaction to each injection was observed and measured. Each of the 12 patients received 13 injections at weekly intervals, but only nine of the 12 control subjects received 13. One subject received 11; two others received only nine. Consequently, the statistical analysis is limited to the findings of the first nine injections. The general description of the findings is, however, based on the 13 injections, because the findings of the last four emphasize what the analysis of the findings of the first nine shows.

## RESULTS

Various differences were found between the cutaneous responses of the schizophrenic patients and those of the control subjects. One of the most striking of these differences is the one between the mean areas of maximum erythematous reaction of the patients to the successive injections and those of the normal subjects to the

corresponding injections. This difference is represented graphically in Figure 1, where the mean area of maximum erythema in square millimeters is shown on the ordinate and the number of the injection on the abscissa. Figure 1 shows that in terms of maximum erythema the mean reaction of the patients to the successive injections was less vigorous than that of the normal subjects. This difference is statistically highly significant with a probability of less than .01 that the difference may be due to chance.

FIGURE I

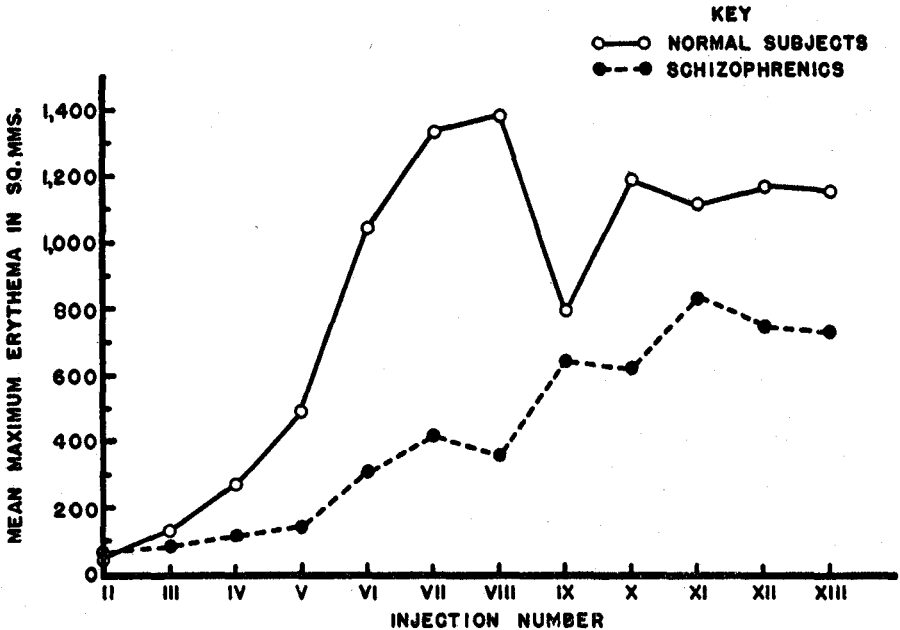


Figure 1. Mean maximum erythematous reactions of schizophrenic male patients and of unselected male normal control subjects to repeated intracutaneous injections of 1:100 guinea pig serum

A further analysis of the data obtained on the successive injections indicates that a process of sensitization was being activated and developed by the repeated injections. To emphasize this finding, the successive data on the patients in Figure 1 have been connected with a broken line and those on the normal subjects with an

unbroken line. An inspection of the two sets of data reveals that, during the first half of the experiment, the mean maximum erythema increased with each succeeding injection. This finding suggests that a sensitization to foreign protein was being developed. The validity of this finding gains greater weight if one considers the results obtained by an analysis of variance which was applied to the present data. This analysis shows: (1) that the responses of a given subject to the various injections are highly consistent; and (2) that the interindividual consistency of the groups is highly significant. The probability that either of these findings is due to chance is also less than .01.

It should be noted that the erythema of the delayed reaction is much more inflammatory in nature than that of the immediate reaction. Despite this difference between the respective erythemas of the delayed and the immediate reactions, no distinction was made between them so far as the measure of maximum erythematous reaction was concerned. This measure, which is quite valid from the operational point of view, was used to simplify the statistical handling of the data. This measure does, however, have the disadvantage of not bringing out all the details of the difference found between the reactions of the patients and those of the normal subjects. It will be convenient, therefore, to point out some of those details at this juncture.

In the first place, the patients and the normal control subjects differed in the same general way with respect both to the delayed and to the immediate reactions. That is, the patients' reactions were less than those of the normal controls, irrespective of whether the groups were compared with regard to the immediate reaction alone or the delayed reaction alone.

In the second place, three of the 12 patients did not have an immediate reaction to any of the 13 injections whereas all the control subjects had immediate reactions to the last four injections. Hence, in terms of immediate reactions, the mean sensitization of the patients after the thirteenth injection was less than that of the control subjects after the tenth. This difference gains added significance, considering the fact that an immediate reaction indicates a greater degree of sensitization than does a delayed reaction.

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HISTAMINE PHOSPHATE

The difference found between the reactions of the patients and those of the control subjects could be due, either to a difference between their respective local vascular responses or to a difference between their respective responses to intracutaneous injections of foreign protein as such. If the former were the case, then the reactions of the patients to intracutaneous injections of a solution of histamine should differ from those of the control subjects in the same manner as their reactions to intracutaneous injections of foreign protein have been found to differ from those of the subjects. This is the more so, because there is a great similarity between a reaction to an intracutaneous injection of histamine and an immediate reaction to an intracutaneous injection of foreign protein. Furthermore, it is held by some investigators that an immediate reaction is due to the H-substance liberated in the local reaction to the injected foreign protein.

The local vascular responses of the patients were tested in the following preliminary manner. Three days after the tenth injection of guinea pig serum each patient received an injection intracutaneously in the left forearm of .1 cc. of a 1:3,000 solution of histamine phosphate. Each patient reacted to this injection with a wheal and a surrounding erythematous flare. These cutaneous reactions were measured several times during the course of their rise and decline, just as were those to the injections of guinea pig serum. No positive relationship was found between a patient's maximum reaction to the injection of histamine and his maximum reaction to the tenth injection of guinea pig serum. The absence of a positive relationship between the reactions to the histamine and to the guinea pig serum demonstrates that the difference found between the reactions of the patients and those of the control subjects to the guinea pig serum was probably due to a difference between their respective responses to the guinea pig serum specifically and not to a difference of the peripheral vasomotor mechanism in general.

## DISCUSSION

The finding that schizophrenic patients are in general hyposensitive to foreign protein can be used in different ways in the further study of schizophrenia. Angyal, Freeman and Hoskins<sup>4</sup> have already suggested that various functions in schizophrenia be represented in the form of a profile which would show what functions were involved and to what degree. The cutaneous reaction to repeated intracutaneous injections of a foreign protein can be added to the proposed profile of functions to be considered. On the other hand, schizophrenic patients can be studied, with respect to any function in which they are hyporeactive, by contrasting and comparing them with a selected group of subjects who are hyperreactive in the particular function. This is especially easy in the case of the schizophrenic's hyposensitivity to foreign protein, because there are many persons who are hypersensitive to foreign protein, that is, those who have hay fever or extrinsic asthma. The writer has already contrasted and compared schizophrenic patients with extrinsic asthmatic patients in a paper on the antagonism between schizophrenia and extrinsic asthmas.<sup>7</sup> In fact, the finding that schizophrenic patients would prove to be generally hyposensitive to foreign protein was predicted in terms of the hypothesis set forth in another study that there is a fundamental physiologic difference between those persons who have schizophrenia and those who have hay fever or extrinsic asthma. It is felt that the comparison of immunological reactions is a promising approach to the biological antagonism between certain pathological conditions and between certain forms of constitution.

## SUMMARY

1. The cutaneous responses to intradermal injections of guinea pig serum, repeated weekly for 13 weeks, have been studied in a group of 12 schizophrenic male patients and in a group of 12 unselected male control subjects.
2. In all patients and in all normal controls, a process of sensitization was developed by the successive injections.
3. It was found that the mean areas of maximum erythematous skin reaction of the patients to the successive injections were significantly less than those of the normal control subjects.

4. One must distinguish between immediate and delayed skin reaction. The former indicates greater sensitivity. All control subjects had immediate reaction to the last four injections, whereas three patients did not have immediate reaction to any of the 13 injections.

5. In order to determine whether the difference between patients and normal controls is due to a difference in their local vascular mechanisms or to their sensitivity to foreign proteins specifically, an intracutaneous injection of histamine was given to each patient. No positive correlation was found between the reaction to histamine and the reaction to guinea pig serum. This finding suggests that the differences found between patients and control subjects are actually differences of immunological reactions.

6. The hyposensitivity of the schizophrenic patients to foreign protein is a special manifestation of their general hyporeactivity.

7. It is suggested that the comparison of immunological responses may be profitably used in the study of biological antagonism between various pathological conditions.

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