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Immunity and Schizophrenia

A Survey of the Ability of Schizophrenic Patients to Develop an Active Immunity Following the Injection of Pertussis Vaccine

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IT has been demonstrated in recent years that hospitalized schizophrenic patients tend to react to environmental stresses in an abnormal manner not only on the psychologic level but also on the physiologic level. Whereas in a healthy normal subject the adrenal gland will respond to stresses with increased activity and increased circulating adrenal cortical substances, the schizophrenic patient more often responds with no increase, or a decrease in adrenal activity (5, 8, 13). The peripheral end-results of this relative inactivity of the adrenal gland in the schizophrenic subject include modifications in the metabolism of lymphocytes (noted clinically by a disturbance of the diurnal curve of total circulating lymphocytes) and a failure of the total circulating lymphocytes to decrease in number following exposure to a stress situation. Chase, White, and Dougherty have reported an intimate relationship between lymphocytes and immune substances, and have extracted specific antibodies from lymphocytes and have produced in the laboratory significant increases in antibody titres following the injection of adrenal cortical extract (2). Because of these findings it was decided to make the survey reported herein. No similar study has been made to our knowledge. Inasmuch as a) schizophrenic patients demonstrate a lower rate of breakdown of lymphocytes, and b) antibody production and release is closely related to lymphocyte metabolism, it is reasoned that one might not find so high a serum titre of antibodies following a course of immunization in the schizophrenic patients as in a normal control group. Other factors, such as previous contact with the antigen and nutritional state must also be considered, and will be discussed below.

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Clinical Study

A series of 22 patients and 17 controls have completed a course of "hyperimmunization" with Plain Pertussis Vaccine, consisting of four weekly injections of the vaccine, beginning with 1 cc., and increased to 2 cc. after the first week, receiving a total of 7 cc. of the vaccine, containing 15,000,000 organisms per cc.[4] Serum was taken from the subjects weekly for eight weeks and antibody titres determined at the Massachusetts Division of Biologic Laboratories by one of us (J.C.S.). Total serum nitrogen values were determined on 16 patients and the controls, using the micro-Kjeldhal method.

Serum for assay is diluted in 0.85% saline. 0.5 ml H. pertussis antigen is added to each tube containing 0.5 ml serum dilution and incubated 1 hour in 37° C. water bath and overnight in a refrigerator. Normal globulin and hyperimmune globuline of known titres are used as reference standards. Antigen controls and serum controls are also included. The last tube with a 1+ reaction is taken as the titre of the serum.

The H. Pertussis antigen is prepared from Strain #484 Phase I H. pertussis, Philadelphia Serum Exchange. The antigen is freshly prepared every two weeks, and is used without preservatives.

Pertussis vaccine was chosen as the immunizing agent because of its safety of administration, the availability of a well-standardized method of titration, and because there has been developed a

[4] The technique of "hyperimmunization" has been developed by McGuinness and co-workers at the Philadelphia Serum Exchange, Philadelphia, Pa. See J. Pediat. **19**: 638, 1941.

TABLE I.
PATIENT SERIES

Patient number	*Pertussis history*	*Diagnosis*	*Age*	*Duration of illness (yr.)*	*Duration of hosp. (yr.)*	*Max. serum titre (recip.)*	*Total serum N (mg. %)*
1	pos.		25	1	.8	120	1072
2	pos.	D.P.,	36	12	11.0	100	850
3	no ans.	other	21	2	2.0	360	992
4	pos.	types	33	7	6.0	480	1092
5	no ans.		36	10	1.5	880	1020
6	pos.		32	5	5.0	60	876
7	pos.	D.P.,	29	4	2.3	50	1030
8	no ans.	paranoid	34	10	8.3	240	....
9	pos.		35	10	2.3	800	1000
10	no ans.		45	10	9.0	20	....
11	no ans.		35	12	12.0	80	848
12	no ans.	D.P.,	38	10	8.3	160	....
13	pos.	catatonic	30	9	1.0	240	828
14	pos.		26	5	4.0	360	1020
15	pos.		18	5	1.0	40	952
16	neg.	D.P.,	18	1	.4	80	....
17	pos.	hebephrenic	36	9	9.0	160	948
18	neg.		37	10	7.0	120	884
19	no ans.		30	5	5.0	160	....
20	pos.		28	3	2.0	400	1106
21	no ans.	D.P.,	24	3	1.3	240	1060
22	no ans.	simple	40	12	3.0	180	....

technique of hyperimmunization with this agent by McGuinness and co-workers which yields very high maximum titres, with a relatively great spread of the titre values in large samples of the adult population.[5] This immunizing agent has one disadvantage, that the factor of previous exposure to

[5] Plain Pertussis Vaccine has been supplied through the courtesy of Parke-Davis and Co., Detroit, Michigan.

TABLE II.
CONTROL SERIES

Control number	*Pertussis history*	*Age (yr.)*	*Maximum serum titre (recip.)*	*Total serum N (mg. %)*
1	prob. neg.	27	640	1138
2	pos.	24	1280	1090
3	neg.	24	80	1108
4	pos.	35	320	1090
5	pos.	22	1280	1100
6	neg.	24	320	1088
7	pos.	24	1280	1125
8	prob. pos.	33	160	1120
9	pos.	30	160	1060
10	neg.	27	320	1210
11	neg.	27	320	....
12	pos.	33	560	1020
13	neg.	31	480	1052
14	neg.	24	640	984
15	pos.	34	240	1000
16	prob. neg.	25	80	....
17	pos.	24	320	....

the organism must be considered as an experimental variable.

The patients chosen were a representative sample of male schizophrenic patients taken from the Research Ward and Male Wards of the Worcester State Hospital. They range in age from 18 years to 45 years, in duration of hospitalization, from four months to twelve years. All subtypes of schizophrenia are included. Table I includes the pertinent data on the patient series.

The control group included 17 healthy young laboratory workers and medical students. This group was not living an institutional life and was slightly younger than the patients. Data on this group appear in Table II.

Results

The mean of the maximum titres obtained over the eight-week period of injection and sampling for the patients was 1:242 with standard deviation of ±1:230 (Table III). This deviation reflects the wide spread in titre values noted in Table I. The same mean for the control group is 1:504, S.D.±1:408. The difference between these means is highly significant, with a p-value of .008.

Inasmuch as the scale of titres follows a geometric progression (1/10–1/20–1/40–1/80) rather than an arithmetic progression it is well to determine the mean of the logarithims of the reciprocals of the titre values. This compresses the range of the series, gives the high and low titres less significance and makes the figures more in accord with the method of titration of limits. The standard deviation becomes smaller. Treated in this preferred manner, the significance of our data is increased. (Table III) Thus it appears from the data of our small series that the schizophrenic patient does not respond to antigenic stimulation to the same degree as the normal person.

TABLE III.
STATISTICAL DATA

PATIENT SERIES	
Arithmetic mean of the reciprocal of the maximum serum titres	242
S.D.	±230
$S.E._m$	± 49
Logarithmic mean of the reciprocal of the maximum serum titres	2.2071
S.D.	± .4030
$S.E._m$	± .0881
CONTROL SERIES	
Arithmetic mean of the reciprocal of the maximum titre values	504
S.D.	±408
$S.E._m$	± 99
Logarithmic mean of the reciprocal of the maximum serum titre values	2.5581
S.D.	± .3862
$S.E._m$	± .0937
DIFFERENCE BETWEEN THE MEANS	
Difference between the arithmetic means	262.
$S.E._d$	110.
C.R.	2.38; p = .008
Difference between the geometric means	.3510
$S.E._d$	.1284
C.R.	2.74; p = .003

Let us now examine the patient series in more detail (Table IV). It appears that no significant correlation exists between maximum titres and age of patient or duration of illness. The latter category—arrived at through careful study of individual records—has questionable value or meaning. A figure which has definite meaning, however, is duration of hospitalization, which represents that

TABLE IV.
CORRELATIONS WITHIN THE PATIENT SERIES

Correlation coefficients (r), and probability values (p)* for the higher correlations, for correlations between maximum titre values and the following variables within the patient series, using the *logarithmic scale* of titre values:

Age	*Duration of illness*	*Duration of hospitalization*	*Total serum nitrogen (mg. %)*
+.09	−.04	−.34 (p = .10)	+.45 (p = .05)

Correlation coefficient (r) between duration of hospitalization and total serum nitrogen:

−.58 (p = .01)

* R. A. Fisher, Statistical Methods for Research Workers. Oliver and Boyd, London, 1936. p. 167.

definite period that the patient has required and received intramural institutional care. There is a low positive correlation between duration of hospitalization and maximum titre value. The institutional state of the patients seems to be reflected by the total serum nitrogen value, and a similarly small positive correlation exists between it and the maximum titre value.

Of great interest is the higher and more significant correlation between total serum nitrogen and duration of hospitalization, which suggests that this group of patients have developed a protein deficiency over the years of institutionalization. This may be due to factors peculiar to this group of patients, (e. g. failure of the protein synthesis mechanism) and is being further investigated.

With regard to diagnostic categories, it appears that those patients with relatively intact capacity to respond with appropriate affect to their environment, diagnosed "other types," have a mean titre of 1:388 (Table V), the paranoid group averages

TABLE V.

SUBTYPES OF DEMENTIA PRAECOX

Subtype	*Mean titre* (*recip.*)	*Mean age* (*years*)	*Mean duration of hospitalization* (*years*)	*Mean total serum nitrogen* (*mg. %*)
Other types ($n = 5$)	388	30	4.3	1005
Paranoid ($n = 5$)	234	35	5.4	969 ($n = 3$)
Catatonic ($n = 4$)	210	32	6.2	899 ($n = 3$)
Hebephrenic ($n = 6$)	160	28	4.1	975 ($n = 4$)
Simple* ($n = 2$)	—	—	—	—

*Table I. contains the individual data on these two patients.

1:234, the catatonic group 1:210, hebephrenic group only 1:160. These differences, though in no way statistically significant, seem perhaps to suggest some fundamental difference in the level of biologic reactivity between the hebephrenic group on the one hand (farthest from normal) and, the "other type" group on the other, (closest to normal). This latter group generally enjoy a more favorable prognosis at Worcester State Hospital.

Discussion

From our small series of patients and controls there has appeared a statistically significant difference in the response of the two groups to antigenic stimulation. Are we to infer therefrom that this difference is, indeed, specifically related to the specific endocrine malfunction of the patients? Many factors must be discussed and further investigated before such a conclusion can be reached.

Let us first consider the laboratory problems. The technic of titration has been carefully controlled. Each individual titration was checked by additional titrations and by further serial dilutions between the extremes of the initial dilution. The reliability of the over-all results was checked when completing the control series by sending paired samples, with their identity concealed, to the laboratory (Table VI). Analysis of these pairs, in-

TABLE VI.

LABORATORY VARIABILITY

Eighteen pairs of identical serum samples, arranged from low to high titre levels:

1.	less than 1/10 vs. less than 1/10
2.	less than 1/10 vs. less than 1/10
3.	less than 1/10 vs. less than 1/10
4.	less than 1/10 vs. less than 1/10
	100% agreement
5.	1/10 vs. 1/10
6.	1/10 vs. 1/20
7.	1/10 vs. 1/20
	33.3% agreement
8.	1/40 vs. 1/80
	no agreement
9.	1/80 vs. 1/80
10.	1/80 vs. 1/80
11.	1/80 vs. 1/160
	66.7% agreement
12.	1/160 vs. 1/320
13.	1/160 vs. 1/320
14.	1/160 vs. 1/320
(15.	1/160 vs. 1/1280*)
	no agreement
16.	1/320 vs. 1/640
	no agreement
17.	1/640 vs. 1/640
18.	1/640 vs. 1/640
19.	1/640 vs. 1/640
	100% agreement

*This pair was rechecked internally and the large titre difference remains. The sample is a fourth week sample; the third week titre was 1/160, and the fifth week was 1/640. We conclude that the lower titre value is the "correct" one, and that the higher reading (1/1280) results from faulty labelling or handling of the sample before it reached the laboratory. This pair is disregarded in our evaluation of variability resulting from the titration technic.

cluding both high and low serum titres, reveal that there are approximately 3 chances out of 4 that the reported titre value is the "correct" one, and the odds approach 100 per cent that no variation greater or less than the next dilution will occur.[6]

This factor of laboratory variation is being further investigated in connection with another study.

The problem of "institutionalization" must be considered. This entails such factors as intramural sedentary life and poor dietary intake as factors per se in causing a lowered response to the antigen. The positive correlation found between a) duration of hospitalization and maximum serum titre levels, and b) maximum serum titre and total serum nitrogen and the higher correlation between length of hospitalization and serum nitrogen level are suggestive. Cannon *et al.* have demonstrated the importance of proteins for "maturation of the globulin matrix," and antibody formation (1). However, in our series we are not dealing with such marked protein deficiencies as he produced in the laboratory. The standard hospital diet is under the supervision of a dietitian and contains adequate supplies of essential proteins. The majority of patients on the research service had been receiving supplemental feedings and vitamins during or shortly before the immunization period. A group of patients from the General Wards of the Hospital must be studied to investigate the relationship, if any, between duration of hospitalization per se and serum nitrogen level. It is believed that this correlation may prove to be peculiar to this schizophrenic group of patients, and is related to the general "sluggishness" of their physiologic mechanisms, already noted in response to stress and response to replacement therapy, both hormonal and nutritional (9, 10). McGuinness has hyperimmunized a group of chronically institutionalized individuals in a Pennsylvania school for the feebleminded, and has found no essential difference from his large adult series in their immunologic response (11). A similar study is now under progress at the Walter E. Fernald State School, Waverley, Mass., under the direction of Dr. Maximilian Weinberger. This study should clarify this moot question of "institutionalization."

Questionnaires were sent to patients' families and given to the control subjects. Fourteen answers were received from patients, giving 11 positive histories of whooping cough, 2 negative histories, 1 "cannot recall." The mean titre value for the patient giving a positive listing is 1:256, and for the remaining 11 patients 1:229, an insignificant difference, even if all not answering had not had whooping cough. Of the 17 controls, 17 answers were obtained with 8 positive histories and 3 questionable histories of childhood whooping cough. The mean of the maximum titre values of those giving positive histories is 1:640, the mean of the remaining number of controls is 1:338. This difference is of questionable significance.[7]

The initial pre-injection titres of patients and controls give some indication of past or recent exposure to whooping cough. With a more sensitive technic of titration, McGuinness reports that 85 per cent of his adult population sample have initial titres of 1:40 or higher, only 8.8 per cent showing titres of less than 1:20, which suggests wide exposure to the antigen (11). One of our control subjects had an initial titre of 1:100, suggesting recent exposure and attained a maximum titre of 1:5120. Inasmuch as the initial titre of all patients was less than 1:20, this subject is not included in our control group. From the above data, it does not appear that the significant difference found can be attributed to selective early or recent exposure to pertussis antigen.

Since the inception of our study several investigators have attempted to confirm the original findings of Chase, White, and Dougherty (3, 4, 7, 12, 14, 15). These efforts have failed to demonstrate, however, that increased amounts of adrenal cortical extract will either consistently increase a preexisting antibody titre or cause consistent significant enhancement of an antibody response to a specific antigen. The reasons for this failure to confirm the original observations are obscure, and may be due simply to differences in the various experimental designs. However, it appears to us that many more factors are involved in the relationship of the adrenal glands to immune mechanisms than simply the previously mentioned lymphocyte-storage-and-destruction mechanism. Protein metabolism itself, and the capacity of the liver and reticulo-endothelial

[6] One pair, which failed to check to one dilution (1:160 versus 1:1280) has been re-checked internally. The discrepancy occurring is the result of faulty handling or labelling of the higher titre specimen before it arrived at the laboratory.

[7] One questions the statements of the controls, when only 8 give a positive history of childhood pertussis, despite the well-known ubiquitousness of pertussis. Holmes states, "the medical histories of adult patients show in almost every instance, a previous attack of whooping cough." He further cites studies which reveal that only ten to thirty percent of pertussis cases are ever reported to public health authorities in certain communities. (See Holmes, W. H.: *Baccillary and Rickettsial Infections.* New York, Macmillan, 1940, p. 400).

system to synthesize the complex "globulin matrix" which represent antibodies, antibody precursors, complement, and so forth, seems definitely related to adrenal function. With special reference to the total blood nitrogen studies mentioned above, we wonder if we are not witnessing relative defects in protein synthesizing mechanisms in those of our patients and controls who did not respond to the antigenic stimulus, which may in some part be related to "sluggish" activity of that particular adrenal hormone system involved in protein metabolism. This hypothesis will require much further work for elucidation or verification.

Certain of our subjects were given a glucose tolerance test following the regular test period, with serum samples being drawn at half, one, six, and twenty-four hour intervals for pertussis antibody titrations. The glucose tolerance test has been demonstrated to be a stimulator of adrenal activity, accompanied by an increased lymphocyte destruction (6). Several subjects showed slight but insignificant changes in antibody levels, while in the remainder there was no change. It is yet to be demonstrated in human beings that increased circulating adrenal hormone will cause an increase in serum levels of already-present antibodies.

Despite the factors which clearly separate the patient and control groups, such as hospitalized existence, and the presence of demential praecox, we find great variation within the groups, with great spread and overlapping of responses. This wide range of individual responses has been noted by McGuinness in his large series of healthy subjects (11). Several of our controls had maximum titres of 1:80, while several patients had titres of 1:880. Nevertheless, our results do demonstrate a statistically significant difference between the means. The cause of this difference and of the great variation of individual responses remains obscure and awaits greater understanding of the biology of the individual, and the role of hormone mechanisms in immuniologic phenomena and cellular metabolism.

Summary

1. A group of 22 male schizophrenic patients and a group of 17 healthy male control subjects have been given a course of hyperimmunization to Pertussis Vaccine.

2. A statistically significant different ($p = .003$) exists between the abilities of these two groups to develop high serum antibody titres.

3. Internal examination of the patient series reveals that duration of hospitalization and blood nitrogen level may in some way be related to this difference. In the patient series there is a slight negative correlation between antibody titre and duration of hospitalization ($r = -.34$), and a positive correlation between antibody titre and total serum nitrogen ($r = +.45$).

4. There is a higher and more significant negative correlation between duration of hosiptalization and total serum nitrogen ($r = -.58$). This suggests a faulty protein metabolism in this group of patients, which may have in some part an exogenous nutritional origin.

5. We wonder, however, whether we are not witnessing relative defects in protein synthesizing mechanisms which may in some way be related to the general "sluggishness" of the hormonal and metabolic mechanisms commonly found in schizophrenic patients.

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