RHEUMATOID FACTORS IN AN ACUTE PSYCHIATRIC POPULATION

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The existence of agglutinating substances reactive with autologous and isologous human gamma globulin (γG) has been recognized for some time. These substances were first found in patients with rheumatoid arthritis and were consequently termed "rheumatoid factor" (RF). It is now clear that rheumatoid factor is not specific for rheumatoid arthritis, but occurs in individuals with a wide variety of other diseases characterized by inflammation, infection, and/or granulomatous formation. Hepatitis, primary biliary cirrhosis, leprosy, syphilis, and subacute bacterial endocarditis are but a few of the other diseases unrelated to rheumatoid arthritis in which some degree of RF activity has been observed. RF has been detected in a high proportion of aged individuals, and is known to occur occasionally in younger persons. Experimentally, rheumatoid-like factor has been induced in rabbits after repeated immunization with various antigens. Since rheumatoid factors derived from various human sources share the ability to react with some form of γG immunoglobulin, they have been sometimes referred to as "anti-γG factors".

As part of a survey of the presence of rheumatoid factor in various populations, it was decided to examine patients newly admitted to an acute psychiatric voluntary hospital who were free of coexisting physical illness, known to be associated with RF, and who had not been subjected to long periods of institutional confinement just before testing. This study was originally prompted by the casual observation of transient RF activity in a patient during a period of severe depressive psychosis.

Patients and Methods

The psychiatric study population consisted of 86 consecutive admissions to the Mount Sinai Hospital Psychiatric Service. Clinical diagnosis included 45 cases of schizophrenia, 27 of endogenous depression, and fourteen of psychoneurosis or character disorders. Patients with suspected rheumatoid arthritis, systemic lupus erythematosus, or other apparent musculoskeletal diseases were excluded. Blood samples were obtained within 7 days after admission.

Control groups consisted of apparently healthy hospital employees and laboratory personnel, and a group of patients attending the diabetes clinic of the Mount Sinai Hospital.

Before testing all sera were adsorbed with washed, packed, uncoated sheep erythrocytes overnight in order to remove heterophil antibodies, and were incubated at 56°C for 30 minutes in order to inactivate complement. Sera were then tested for rheumatoid factor activity with two procedures:

(a) The latex slide test, employing a commercial test reagent (RA-Hyland) at a single serum dilution of 1:20.
(b) The tanned sheep cell (TSC) test of Heller, Kolodny, Lepow, Jacobson, Rivera, and Marks (1955).

The details of preparations of tanned, γG-coated sheep cells have been previously described (Oreskes, Singer, and Plotz, 1963). The test sera were 2-fold serially diluted, starting at a serum dilution of 1:20. Equal volumes of 0·25 per cent. tanned human-γG-coated sheep cells were added to each tube and the mixture was kept overnight in the refrigerator. The next day tubes were examined for agglutination according to the pattern of the sedimented cells (Jacobson, Kammerer, Wolf, Epstein, and Heller, 1956). A titre of 1:40 or greater was considered positive.

Results

Psychiatric Group.—42 positive results (49 per cent.) were obtained with the TSC test (Table I, opposite). There was no difference in the frequency of positive results among males as compared with females. Positive TSC tests were obtained in all diagnostic categories (Table II, opposite). Of fourteen patients with a clinical diagnosis of psychoneurosis or character disorder, eight (57 per cent.) were positive. Of 45 patients diagnosed as having schizophrenia, seventeen (30 per cent.) were positive. The highest frequency of positive tests (63 per cent.) was found among patients with endogenous depression.

In contrast to the results obtained with the TSC test, only eight positive reactions (9·3 per cent.) were obtained with the latex slide test. This positive frequency was similar to that of 8·2 per cent. reported by Fessel (1961), using the same procedure in a survey of anti-γG factors among 1,109 unselected chronic psychiatric patients in a state hospital.
The median TSC titre for the psychiatric group as well as for the control groups was 1:80 (Table III). This is in contrast to findings in definite and classical rheumatoid arthritis where a median titre of 1:5,120 has been reported (Oreskes and Siltzbach, 1965). The low titres found in the present psychiatric group, however, are comparable to those found in diseases other than rheumatoid arthritis (Bartfeld, 1960), as for example sarcoidosis (Oreskes and Siltzbach, 1965, 1968).

When the TSC procedure was performed with omission of serum heating at 56°C for 30 minutes, an average 2-fold increase in titre, i.e. one tube, resulted. In addition, seven sera were converted from negative to positive (median titre 1:40). Thus, omission of the heating step increased the total frequency of positive tests among the psychiatric patients to 49 of 86 (57 per cent.). This apparent sensitivity of some rheumatoid factors to heat has been noted for such factors derived from individuals with hypertension or schizophrenia (Brooks, Malik, and Cobb, 1964).

The high frequency of RF activity among psychiatric patients was not a consequence of increased age (Table IV). Among RF-positive as well as RF-negative patients, the median age was found to be in the fourth decade. Of the 86 patients studied, 76 were under the age of 60 years, and of these 36 (46 per cent.) were TSC positive.

Control Group.—The 79 hospital personnel yielded ten positive TSC tests (13 per cent.). Of the 29 diabetics, three (10 per cent.) were similarly positive. In these groups as in the psychiatric group, the number of positive results obtained with the TSC test was strikingly higher than that obtained with the latex slide test.

The difference in frequency of TSC positive tests in the psychiatric series as compared with the control group was statistically significant ($\chi^2 = 17.11; P<0.001$). There was no significant difference in positive tests between the healthy controls and diabetics. The higher proportion of positive TSC tests in the psychiatric group could not be ascribed to transient respiratory or other viral infections (Dresner and Tromby, 1959; Svec and Dingle, 1965).
The macroglobulin nature of the agglutinating factors in the psychiatric patients was demonstrated by treatment of TSC-positive sera with 0.1 M mercaptoethanol which in all cases abolished agglutinating activity. Cellulose acetate electrophoresis revealed no significant differences in serum proteins between TSC positive and negative sera. Among patients whose drug histories could be ascertained, there was no correlation between the ingestion of potentially hepatotoxic drugs (such as phenothiazines, monoamine oxidase inhibitors, or iminodibenzyl antidepressants) and the finding of rheumatoid factor activity (Table II).

Discussion

The frequency of positive RF tests obtained in the present study with the TSC procedure is far in excess of the frequency of such positive tests obtained by Fessel (1961) with the latex slide test. This seems primarily to be due to the greater sensitivity of TSC test. That this is so is suggested by the nearly identical results obtained by us and by Fessel (1961), using the latex test. This marked difference in sensitivity between these two tests has previously been observed in non-rheumatoid disease (Bartfeld, 1930; Oreskes and Siltzbach, 1968).

There are two major technical differences between these procedures which could account for the observed difference in sensitivity. In the latex-fixation test, as well as the latex slide test as opposed to the TSC test, the reagent supernatant contains free non-adsorbed γG. This excess γG could exert an inhibitory effect on small concentrations of rheumatoid factor.

Another important difference is that the γG adsorbed to the latex particles is apparently surface denatured (Singer, Altmann, Goldenberg, and Plotz, 1960). On the other hand, γG adsorbed to tanned sheep cells is a mixture of both denatured (aggregated) and undenatured protein (Singer, Oreskes, and Altmann, 1962). Thus, the immunological specificities of adsorbed γG in the two test systems may not be identical. It may be noted that anti-γG factors with Gm specificity ("Snagg's") do not react with γG-coated latex particles but are detected by RH antibody sensitized human red cells (Steinberg, 1962).

The significance of the present findings remains to be assessed. It must be emphasized that the findings of rheumatoid factor associated with psychiatric disease in no way implies "autoimmunity" or "connective tissue disease" as being operative in the aetiology of pathogenesis of the mental illnesses.

Fessel (1962) has reported significant elevations of serum S19 macroglobulins in patients with functional mental illness. Further, Fessel and Forsyth (1963) have shown that electrical stimulation of the rat hypothalamus results in an increase in γG serum levels. The question arises whether hypothalamic phenomena associated with psychiatric illness in the human can similarly cause an aberration in immunoglobulin synthesis which in turn may result in the production of anti-γG antibodies, but some as yet unknown mechanism. Another possibility is that some underlying somatic changes are in fact responsible for both the mental illness and the immunological abnormalities.

Thus rheumatoid factor, originally thought to be specific for rheumatoid arthritis, and later found in a wide variety of other physical diseases, appears to be present also in a high percentage of patients with psychiatric disorders. These findings support the concept that the production of rheumatoid factor represents a common immunological response to ostensibly altered γG. If so, then alteration of γG would seem to occur in a wide variety of diseases by mechanisms that are as yet unclear.

Summary

86 patients with various mental illnesses, newly admitted to an acute psychiatric ward, were examined for the presence of rheumatoid factor in their serum. Of these, 42 (49 per cent.) were positive with the tanned sheep cell test in titres of 1:40 or above. Titres tended to be low, with a median value of 1:80, in contrast to the much higher titres generally encountered in patients with rheumatoid arthritis. No correlation between age or sex and the presence of rheumatoid factor activity was seen. Similarly, no transient viral infections or ingestion of potentially hepatotoxic drugs could not be related to these findings. The tanned sheep cell test proved to be far more sensitive in detecting rheumatoid factor in psychiatric patients than did either slide or tube tests employing latex particles. In the present state of our knowledge, the finding of rheumatoid factor in a high proportion of patients with acute psychiatric disease cannot be interpreted as meaning that autoimmune processes are operative in the aetiology or pathogenesis of these disorders.

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Facteurs rhumatoïdes dans des cas psychiatriques aigus. 

RÉSUMÉ 
On rechercha le facteur rhumatoïde dans le sérum de 86 sujets nouvellement admis dans un service de psychiatrie pour affections aiguës. Dans 42 cas (49%) la réaction de Waaler-Rose fut positive à 1/40 ou plus. Le titre tendait à être bas, avec une moyenne de 1/80, contrastant avec le titre généralement beaucoup plus élevé des malades ayant une polyarthrite rhumatoïde. On ne trouva aucune corrélation entre âge, sexe et présence du facteur rhumatoïde. De même, on ne put imputer ces résultats à des affections virales transitoires ou à l'ingestion des médicaments potentiellement hépatotoxiques. La réaction de Waaler-Rose s'avéra beaucoup plus sensible pour détecter la présence du facteur rhumatoïde chez ces malades mentaux que le test au latex pratiqué sur lame ou en tube. Dans l'état actuel de nos connaissances la présence du facteur rhumatoïde dans une grande proportion des cas de maladie mentale aiguë ne peut pas être interprétée comme la preuve qu'un processus d'autoimmunité intervient dans l'étiologie ou la pathogénie de cette maladie.

Factores reumatoídes en casos psiquiátricos agudos.

SUMARIO 
Se buscó el factor reumatoíde en el suero de 86 casos agudos nuevos admitidos en un servicio de psiquiatría. En 42 casos (49%) la reacción de Waaler-Rose fue positiva a 1/40 o más. El título tendía a ser bajo, con un promedio de 1/80, contrastando con el título generalmente mucho más elevado en enfermos con artritis reumatoide. No se encontró correlación alguna entre la edad, el sexo y la presencia del factor reumatoide. Tampoco se relacionaron estos resultados con afecciones virales transitorias o medicación potencialmente hepatotóxica. La reacción de Waaler-Rose fue mucho más sensible para detectar la presencia del factor reumatoide en estos enfermos mentales que la reacción de latex, hecha sobre un portaobjetos o en un tubo. En el estado presente de nuestros conocimientos, la presencia del factor reumatoide en una gran proporción de los casos de enfermedad mental aguda no puede interpretarse como prueba de un proceso de autoinmunidad en la etiología o la patogénesis de esta enfermedad.