The effect of neuroleptic drug treatment on plasma fibrinogen concentrations in schizophrenic states

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Reports of a protein anomaly in functional psychoses have been steadily accumulating since the subject was reviewed by Fessel (1962a). As a result, concepts of schizophrenia as a metabolic and autoimmune disorder (Fessel, 1962b; Heath and Krupp, 1967; Heath, Krupp, Byers, and Liljekvist, 1967a, b) associated with a blood factor have been developed. Following the report by Bergen, Koella, Freeman, and Hoagland (1962) that the replacement of the plasma of psychotic patients by serum led to loss of physiological activity after injection into rats, Seal, Swaim, and Eist (1967) examined the plasma fibrinogen content of 13 newly admitted, and 80 institutionalized schizophrenic subjects. The observed increase in both cases was highly significant \( P < 0.001 \) when compared with values derived from 20 normal persons. Their results appeared to exclude hospitalization and physical disease as complicating variables, but the possible effect of drug treatment was not explored.

The present study was designed to repeat the experiment on four controlled groups of patients covering all categories of schizophrenic states, and to determine whether ataractic medication influences their plasma fibrinogen concentration.

METHODS

SUBJECTS Patients were divided between the following four groups of 25 each on the basis of age and clinical history. All were free from known physical disease. Group A (Chronic childhood psychosis) Subjects were diagnosed according to criteria proposed by a Working Party (1961) in this field. All presented with the picture of severe retardation and withdrawal, and their intellectual potential could not be determined. The majority also displayed hyperactivity with mannerisms and stereotyped movements. Their ages ranged from 6 to 16 years. All were residents of the Children's Cottages Training Centre, Kew, Victoria, Australia, and had been institutionalized for an average of six years, the range being one to 15 years. Drug treatment was suspended for one week before blood collection.

Group B (Acute schizophrenia) The patients, aged between 16 and 45 years, presented either at Melbourne University Department of Psychiatry or at the Royal Park Hospital. They included acute exacerbations of previously diagnosed schizophrenia. The criteria for diagnosis were similar to those described for Group C. Most had started phenothiazine treatment before admission to hospital. Blood samples were taken within one week of presentation.

Group C (Chronic schizophrenia) Subjects were between 28 and 60 years old. The length of hospitalization varied between seven and 40 years, the first attack having occurred at least 10 years before admission. The criterion for selection was the establishment of passivity feelings or of a primary delusion; when neither of these symptoms was present a patient who showed at least four of the following five symptoms was diagnosed as schizophrenic: (1) the presence of delusions of elaboration; (2) the presence of schizophrenic thought disorder; (3) the presence of hallucinations; (4) flexibilitas cerea, catatonic episodes, or stereotypes; (5) ideas of reference.

Patients with known brain damage were excluded. They were housed in a ward of a mental hospital and treated uniformly in diet and as uniformly as possible in the regime adopted for their supervision.

Group D (Chronic geriatric schizophrenia) Patients were drawn from female wards of Kew Mental Hospital. Their age range was 51 to 80 years. They had a long history of paranoid and other delusions. The average period of hospitalization was 12 years. It was not possible to relinquish phenothiazine therapy at the time of blood collection.

Normal control groups consisted of mentally healthy individuals matched with patients for sex and as closely as possible for age. The children were outpatients of the Surgical Research Unit, Royal Children's Hospital, Melbourne. Controls for Group D were selected from inmates of Mount Royal Hospital, Parkville, and Greenvale Village for the Aged, Broadmeadows, Victoria. Hospital staff volunteers and blood donors made up the remainder.
The significant elevation of fibrinogen content in acute (Group B) and geriatric chronic schizophrenia (Group D) supports the finding by Seal et al. (1967) of hyperfibrinogenaemia in both newly admitted and institutionalized schizophrenic subjects. It is pertinent to inquire into some possible reasons why significant increases were not reached in the remaining two groups of chronic patients. A few of the factors inadequately controlled by the normal groups include the effects of tranquilizing drugs, hospitalization, aspects of previous history such as stress, and genetic predispositions.

Hospitalization appears to be of little, if any, importance in view of the significant results obtained on the newly admitted patients of Seal et al. (1967), and those of Group B in the present series. It is therefore considered that diet, degree of exercise and activity, and other concomitants of institutional life play no major role in the causation of hyperfibrinogenaemia. No conclusions relating to the relevance of psychological and genetic factors can be drawn from the present study.

Stress has been linked with raised fibrinogen concentrations in two recent publications. Fessel (1965) found that the mean level of dextran-induced plasma turbidity, consisting mostly of precipitated fibrinogen, fell 66% in 18 prisoners when blood taken two weeks after a Parole Board hearing was compared with blood taken in the morning of the hearing. It was concluded that emotional stress, rather than any particular sort of mental disorder, was the prime contributor to the effect. Subsequently, Cameron and Dawson (1967) confirmed that levels of dextran-precipitable fibrinogen in newly admitted patients with depressive symptoms, anxiety states, schizophrenia, and hypomania varied.

## Discussion

### TABLE I

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
<th>Age Mean (yr)</th>
<th>Fibrinogen level Mean (mg/100 ml.)</th>
<th>Significance of difference between means (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>10</td>
<td>12</td>
<td>505</td>
<td>0.11</td>
</tr>
<tr>
<td>controls 15</td>
<td>10</td>
<td>11</td>
<td>452</td>
<td>0.0045</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>27</td>
<td>527</td>
<td>0.12</td>
</tr>
<tr>
<td>controls 15</td>
<td>0</td>
<td>8</td>
<td>397</td>
<td>0.027</td>
</tr>
<tr>
<td>25</td>
<td>0</td>
<td>44</td>
<td>440</td>
<td>0.13</td>
</tr>
<tr>
<td>controls 25</td>
<td>0</td>
<td>10</td>
<td>395</td>
<td>0.013</td>
</tr>
<tr>
<td>0</td>
<td>25</td>
<td>69</td>
<td>618</td>
<td>0.12</td>
</tr>
</tbody>
</table>

### Postprandial Venous Blood Samples

Postprandial venous blood samples were collected and quickly transferred into glass bottles containing 200 i.u. heparin. Plasma fibrinogen contents were performed in duplicate using a method (Brackenridge, 1960) of the heat suspension technique (Stirland, 1956).

### RESULTS

The results of the plasma fibrinogen concentrations in each of the psychotic and control groups are summarized in Table I. Before applying Student's t test to the differences between the means, use of the analysis of variance ratio F test showed that in each group the increases and decreases between sample variances were not significant. In Group D, and particularly in Group B, the differences between the means, of P reached accepted levels of significance. In Group C, while it was possible to examine the mean level of dextran treated and untreated patients, the results were not significant. Phenoetheusine were compared with all 25 subjects for one month, with having blood samples collected. Six-monthly analyses were again performed. Frequency distributions of the plasma fibrinogen levels obtained in Histograms B and C (Fig. 1). Renewal concentration led to an average increase of 39%; red with the mean and S.D. of 613 ± 55 mg/100 ml. represents an average rise of 108 mg/100 ml.

The distribution in Histogram B is bimodal; the mode corresponds to that in Histogram C, which is lower than that in Histogram A, which is the pooled normal groups. Histogram D displays the bimodality evident in B. Thus the 300-399 class interval occurs in rams A, B, and D, while a mode at the 500-599 ml exists in Histograms B, C, and D.
Groups B and D were under greater duress than Groups A and C.

The observation that the increasing extent of medication among the groups is in the order of C, A, B-D—which matches the order of significance C, A, D, and B found in Table I—immediately suggests a correlation between raised fibrinogen levels and the effects of phenothiazine therapy. The data of Fig. 1 confirm this impression. When the patients of Group B were again placed on tranquillizing drugs, the measure rose to a degree not attained by any of the groups. Reintroduction of treatment can be likened to medication of newly admitted patients with acute symptoms, and the reported significance levels of \( P < 0.001 \) and 0.0045 for these groups is consistent with the hypothesis.

The bimodal frequency distributions observed in Fig. 1 can also be explained in this way. The mode at the 300-399 mg/100 ml. interval represents the peak level in health (Histogram A) and after suspension of drug treatment (Fig. 1b). Its presence in Histogram D reflects the number of subjects, mainly in Groups A and C, not receiving phenothiazines. On the other hand, the mode at the 500-599 mg/100 ml. interval represents the peak level in treated patients (Fig. 1c and d). Its occurrence in Histogram B may mean that withdrawal of medication for one month is insufficient time for the fibrinogen concentration to return to normal. It may take several months to restore normal liver function in subjects who have taken chlorpromazine for prolonged periods (Yuwiler, Jenkins, and Du Kaff, 1961).

Several reports have appeared describing changes in the levels of other plasma proteins synthesized by the liver following therapeutic doses of neuroleptic drugs (Trigos and McCullough, 1955; Carver, 1962). So far, however, their specific effect on fibrinogen metabolism has apparently not been investigated. In the absence of evidence of physical disease and of widespread brain damage—which is thought to be conducive to hyperfibrinogenaemia (Elliott and Buckell, 1961)—the pharmacological effect seems the most likely explanation of the results obtained in the four categories.

**SUMMARY**

Plasma fibrinogen concentrations have been measured in 100 schizophrenic patients allocated into four groups: (A) chronic, childhood, (B) acute, newly admitted, (C) chronic, middle aged, and (D) chronic, geriatric. In categories B and D, the mean levels were significantly raised in relation to healthy control subjects matched for sex and age.

All Group C patients had been deprived of tranquillizing drugs for one month at the time of blood
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