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 ateractive 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. Many 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 was 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 Green Vale Village for the Aged, Broadmeadows, Victoria. Hospital staff volunteers and blood donors made up the remainder.
Results

The results indicate that the plasma fibrinogen concentrations in the psychotic and control groups are significantly different, as shown in Table 1. Before applying Student's t test to compare the means, an analysis of variance (ANOVA) was performed to ensure that the variances between the samples were not significantly different. In Group D, and particularly in Group B, the means of P reached high levels of significance.

In Group C, it was possible to examine the effect of neuroleptic drugs on plasma fibrinogen. Phenothiazines were administered to all 25 subjects for one month, and blood samples were collected. The results showed that the means of P were significantly different from those in the other groups. In Group A, the means of P were significantly lower than those in the other groups, suggesting that neuroleptic drugs may have a lower effect on plasma fibrinogen.

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 groups. This finding is significant and indicates the importance of considering neuroleptics as a cause of hyperfibrinogenaemia. The results obtained from the present study are consistent with previous findings and indicate that neuroleptics may be a possible cause of hyperfibrinogenaemia.

Table 1
PLASMA FIBRINOGEN RESULTS IN FOUR GROUPS OF SCHIZOPHRENIC AND CONTROL SUBJECTS

<table>
<thead>
<tr>
<th>Groups</th>
<th>Males</th>
<th>Females</th>
<th>Age Mean (yr)</th>
<th>S.D.</th>
<th>Fibrinogen level Mean (mg/100 ml)</th>
<th>S.D.</th>
<th>Significance of difference between means (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>controls</td>
<td>15</td>
<td>10</td>
<td>12</td>
<td>3</td>
<td>505</td>
<td>118</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>10</td>
<td>27</td>
<td>2</td>
<td>452</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>10</td>
<td>44</td>
<td>8</td>
<td>397</td>
<td>138</td>
<td>0.0045</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0</td>
<td>69</td>
<td>9</td>
<td>395</td>
<td>89</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>25</td>
<td>69</td>
<td>7</td>
<td>618</td>
<td>198</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>25</td>
<td>69</td>
<td>10</td>
<td>509</td>
<td>129</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Discussion

The results suggest that neuroleptics may be a cause of hyperfibrinogenaemia in both acute and chronic schizophrenia. 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 groups. This finding is significant and indicates the importance of considering neuroleptics as a cause of hyperfibrinogenaemia. The results obtained from the present study are consistent with previous findings and indicate that neuroleptics may be a possible cause of hyperfibrinogenaemia.

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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 Kay, 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 hyperfibrinogenemia (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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**FIG. 1.** Frequency distributions of plasma fibrinogen concentrations in (A) 100 normal control subjects pooled from Groups A, B, C, and D; (B) 25 Group C schizophrenic patients, freed from drug treatment for one month; (C) the same 25 Group C patients six months after restoration of treatment; and (D) 100 schizophrenic patients pooled from Groups A, B, C, and D.

widely and bore no relation to diagnostic category. They supplied evidence that it provides a measure which responds to treatment, and advanced the hypothesis that it is a biochemical response to anxiety. The difficulty in ascribing the present hyperfibrinogenaemia to stress lies in establishing that
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REFERENCES

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