Lipid Chemistry and the Psychiatric Patient

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Introduction
A considerable body of knowledge has been accumulated in recent years concerning severe genetic neurological diseases such as Tay-Sachs, Sandhoff's disease, juvenile GM2 gangliosidosis, juvenile GM1 gangliosidosis, chronic Gaucher's disease, and Fabry's disease. Those are in effect genetic sphingolipid-oses (O'Brien et al., 1972). The detection of both homozygotes and heterozygotes is now possible in utero (O'Brien et al., 1972; O'Brien, 1973). Similarly the biochemistry and treatment of disorders such as Parkinson's disease are understood (Hornykiewich, 1973).

When one examines other neurological disorders, much less is known. In schizophrenia, mental depression, or hyperkinesis, there are no demonstrable neuropathological changes, no mode of genetic transmission, and no acceptable animal models (Matthysse, 1973). In these diseases it is necessary to construct a working biochemical relationship based upon the actions of antipsychotic drugs. Matthysse (1973) notes that enhancement of dopamine turnover seems to characterize the antipsychotic drugs of the butyrophen-one, diphenyl butylpiperidine, and phenothiazine classes. They probably act by blocking dopamine receptors. In introducing a symposium on the contributions of neurochemistry to neurology and psychiatry, Robert (1973) noted that normal relations in ganglia must involve a coordinated functioning of different groups of neurons whose transmitters are gamma-amino-butyric acid, dopamine, acetylcholine, and possibly glutamine acid. He states, "It might be expected that, a number of diseases of the basal ganglia will be found associated with the defective functioning of one or another of these neuronal systems." If the defect in any of the systems becomes great enough so that adequate compensatory adjustments within and between the

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neural subsystems cannot be made, physiological or psychological manifestations of this inadequacy must become evident.

Issidorides (1971) notes that the lesion leading to degeneration of nigral neurons, at least in Parkinsonism, may be secondary to the loss of close contacts between capillaries and nigral neurons in the zona compacta. Thus microcirculation must play an extremely important role in all brain regions, and disturbances in the neural vascular relationships must lead to neurological and psychological symptomatology.

The relationship between blood lipids and blood supply to the cerebrovascular system, the cardiovascular system, and the peripheral vascular system has been well documented in the past 20 years. Relationships between serum lipids, stress, and catecholamines have been reported by many investigators (Grundy and Griffin, 1959; Dreyfuss and Czazkes, 1959; Bogdonoff et al., 1964; Gottschalk et al., 1965). As yet unreported are relationships between emotional disturbances, serum lipids, and the general state of intermediary metabolism in the individual. In this report, preliminary observations of these relationships will be presented.

Experimental

Subjects for the study were randomly drawn from an in-house population of a school for emotionally disturbed children. The subjects were 11 individuals who had been classified as psychotic by school psychiatrists without reference to any biochemical laboratory data on the subjects. The subjects consisted of six males and five females, mean age 18.2 years, S.D. 4.17.

Plasma lipid determinations were performed by previously reported semi-automated procedures (Fleischman et al., 1968). The standard errors of the methods were 2.6, 2.4, and 2.6 mg/dL respectively for phospholipids, total cholesterol, and triglycerides. Assays for coenzymes, enzymes, insulin, and intermediate metabolites were performed by clinical laboratories, independent of the laboratory performing lipid determinations by standard clinical laboratory techniques. Trace metal determinations in hair were run by atomic absorption spectroscopy, again independent of the laboratory performing either the lipid or the other biochemical determinations.

Results and Discussion

In Table 1 is given the basic data on the subjects and their plasma lipid values. Nine of the 11 subjects have abnormal blood cholesterol, or phospholipid values, or both. The normal range of phospholipid to cholesterol ratio is 1.00 to 1.20 (Frankel and Reitman, 1963), while the age-specific normal levels for serum cholesterol is below 220 mg/dL for subjects in this age group (National Heart and Lung Institute) and definitely below 200 mg/dL for a nine-year-old male. This normal range for phospholipids depends upon the cholesterol level since one of the prime functions of the phospholipids is as a polar lipid portion in the lipoprotein transport of lipids in the body. A comparison with age-adjusted serum cholesterol levels in the United States (U.S.P.H.S., 1967) for subjects under 24 years of age indicates that in a normal American male population one might expect approximately 13.2 percent to have serum cholesterol values of 220 mg/dL or higher, while for females the percentage would be 15.1 percent. From these data it can be seen that a significant portion of the subjects evidencing mental disturbance also evidenced a concomitant abnormality in lipid metabolism.

A finding of this type requires mechanistic evidence in order to ascertain whether it is strictly coincidental, or whether a relationship could actually exist. Issidorides (1971) had noted that disturbances in the neural vascular relationship must lead to neurological and psychological symptomatology. The nature of the symptomatology most probably depends upon the area in which the disturbance exists. There have been innumerable reports directly linking serum
lipid levels with cardiovascular, cerebrovascular, and peripherovascular diseases. As early as 1961, Cramer (1961) noted alterations in cholesterol and phospholipid ratios in individuals suffering from coronary heart disease. Kahn and Dawber (1966), Slack (1969), Cohen (1959), and Friedman et al. (1962) among many others found that hyperlipoproteinemia with its concomitant increases in cholesterol, phospholipids, and triglycerides is directly related to ischemia and is one of the prime risk factors in coronary artery disease, cerebrovascular disease, and peripherovascular disease. Friedman et al. (1962) indicates newly formed intimal capillaries have increased permeability to lipoprotein molecules leading to atheroma formation with its concomitant ischemia in narrowed blood vessels.

Narrowing of blood vessels with resultant ischemia could lead to neural tissue alterations, but it is known that not only are lipid abnormalities involved in hypercoagulability of blood. Coccheri et al. (1961) reported that lipemia accelerates thromboplatin activation, while Margo-lis (1962) has shown that saturated fatty acids activate Hageman Factor. Hecht and Slotta (1967) reported that glycerophosphatides manifested high blood coagulation-activator activity. Thus from two mechanistic points of view, lipid abnormalities could potentially be implicated in the disturbances of the neural vascular relationship and thus lead to neurological and psychological abnormal symptomatology.

Having noted the relationship between blood lipids and psychosis in this group, it now is of value to examine the relationship of blood lipids to various facets of intermediary metabolism. In view of the work of Kobayashi (1957) in 1957, relating death rate from apoplexy with the trace element composition of water, and subsequent work by Schroeder (1960), Anderson et al. (1969), Roberts and Lloyd (1972), and Crawford et al. (1971) on the same subject, a relationship was sought between serum lipids and the trace element concentration. This search was further reinforced by the work of Cotzias (1969) relating manganese poisoning and DOPA, and the work of Yase (1972) relating degenerative diseases of the central nervous system and particularly amyotrophic lateral sclerosis to elevated manganese, particularly in the presence of elevated calcium concentrations where these metals are absorbed by the body. That these trace elements might in part work through the lipids was suggested by the work of Fleischman et al. (1966, 1967) and Yacowitz et al. (1965) who showed that elevated exogenous calcium exerted

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**TABLE 1**

Comparison of Psychological Diagnosis and Lipid Data on the Experimental Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Cholesterol</th>
<th>Phospholipid</th>
<th>Cholesterol/Phospholipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>F</td>
<td>18</td>
<td>Schizophrenia</td>
<td>267*</td>
<td>282</td>
<td>1.08</td>
</tr>
<tr>
<td>MS</td>
<td>M</td>
<td>15</td>
<td>Schizophrenia</td>
<td>300</td>
<td>128</td>
<td>0.43</td>
</tr>
<tr>
<td>DP</td>
<td>M</td>
<td>24</td>
<td>Schizophrenia</td>
<td>176</td>
<td>160</td>
<td>0.90</td>
</tr>
<tr>
<td>DA</td>
<td>M</td>
<td>23</td>
<td>Schizophrenia</td>
<td>215</td>
<td>204</td>
<td>0.94</td>
</tr>
<tr>
<td>MH</td>
<td>F</td>
<td>15</td>
<td>Manic</td>
<td>138</td>
<td>210</td>
<td>1.52</td>
</tr>
<tr>
<td>LL</td>
<td>F</td>
<td>20</td>
<td>Paranoid</td>
<td>156</td>
<td>170</td>
<td>1.09</td>
</tr>
<tr>
<td>HC</td>
<td>F</td>
<td>19</td>
<td>Schizophrenia</td>
<td>205</td>
<td>176</td>
<td>0.86</td>
</tr>
<tr>
<td>KJ</td>
<td>F</td>
<td>21</td>
<td>Depressive</td>
<td>142</td>
<td>155</td>
<td>1.09</td>
</tr>
<tr>
<td>DU</td>
<td>M</td>
<td>18</td>
<td>Schizophrenia</td>
<td>164</td>
<td>102</td>
<td>0.62</td>
</tr>
<tr>
<td>BE</td>
<td>M</td>
<td>9</td>
<td>Schizophrenia</td>
<td>216</td>
<td>230</td>
<td>1.06</td>
</tr>
<tr>
<td>BF</td>
<td>M</td>
<td>18</td>
<td>Schizophrenia</td>
<td>154</td>
<td>194</td>
<td>1.26</td>
</tr>
</tbody>
</table>

*Abnormalities in boldface.
A significant hypolipidemic effect in both animals and man.

Based upon the reports of Strain et al. (1972) and of Hammer et al. (1971), the trace metal content of the hair was taken as the measure of exposure level and correlated with the lipid levels (Table 2). No significant correlations between serum lipids and trace metals were obtained. This was not completely unexpected in view of the work of Bierenbaum et al. (1969, 1973) which showed that exogenous trace metals did not exert their effect on coronary heart disease through the medium of the serum lipids. Since trace metals act as enzyme activators, control the osmolality of the microenvironment of tissues, and of course are an integral part of the nerve conduction sequence, trace metal concentrations may be highly significant, but through mechanisms other than the lipids.

A suggestion by Leopold and Kremer (1961) that leucocytes were implicated in lipid metabolism prompted an examination of the correlation between leucocytes, cholesterol, and phospholipids (Table 3). It can be seen that the correlation between phospholipid to cholesterol ratio and lymphocytes is statistically significant at the 95 percent confidence level. Although a report by Lenz et al. (1969) showed alterations in leucocytes following triglyceride ingestion in rats, the biological significance of this relationship requires clarification.

From an examination of intermediate metabolic cycles for carbohydrates, lipids, and amino acids, the involvement of adenosine triphosphate, nicotine adenine dinucleotide, and pantothenic acid in these cycles is obvious. Kritchevsky et al. (1960) showed that nicotinic acid enhanced cholesterol oxidation in rat
liver mitochondria, while Carlson and Liljedahl (1963) showed that norepinephrine-induced fatty liver formation was inhibited by nicotinic acid which blocks the catecholamine-induced stimulation of free fatty acid mobilization from the adipose tissue. These comparisons are shown in Table 4. It can be noted that both nicotine adenine dinucleotide levels and pantothenate levels correlate negatively with the phospholipid to cholesterol ratio, P<0.01, and positively with the cholesterol, P<0.05. Again, the biochemical mechanisms involved have yet to be elucidated since these cofactors are involved both in lipid biosynthetic and degradative reactions.

In summary, it can be noted that a direct relationship exists between psychosis and an abnormality in lipid metabolism. Mechanistically this could work by interfering with the blood supply to the neurons either by atheroma formation, or by thrombus formation, or both. Additionally, relationships as yet not mechanistically elucidated appear to exist between metabolic cofactors and blood lipids.

REFERENCES


Dietary Management of Hyperlipoproteinemia: A Handbook for Physicians. Published by the National Heart and Lung Institute, Bethesda, Md.


