ADRENAL LIPOIDS AS SEEN POST MORTEM IN SCHIZOPHRENIA

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DURING an investigation of the morbid anatomy of pituitary and adrenal glands of an unselected series of mental hospital patients (1), it was noted that adrenal sudanophilic material and birefringence were reduced in many cases of schizophrenia. It was therefore decided to make a statistical study of such cases in order to determine if any significance could be attached to the findings and if so, to consider how the facts might be related to present knowledge of schizophrenia.

The adrenal glands were treated as described in our previous paper and the birefringent material seen microscopically under the conditions specified was classified in two grades, No. 1, nil or scanty, and No. 2, moderate or excessive. The term "adrenal lipoid" in this paper refers to birefringent material stainable with Sudan IV. Forty-one cases of schizophrenia were compared with a group of 287 cases of other mental diseases and an obvious deficiency of adrenal lipoids was found in the schizophrenic group (see Table I).

TABLE I
Adrenal Lipoids in Schizophrenia and Other Mental Diseases

	Adrenal Lipoids		
	Grade 1	Grade 2	Total
Schizophrenia	30 (73%)	11 (27%)	41 (100%)
Other mental illness	122 (43%)	165 (57%)	287 (100%)
Total	152	176	328

As the age and sex distribution of cases with schizophrenia differed considerably from those with other mental diseases, and in addition there was some evidence that liver damage was more common among schizophrenics, it was decided to take a sample of cases which had been paired for age, sex and liver damage, but otherwise selected at random. The constitution of this sample is shown in Table II. Table III shows that adrenal lipoids were found

https://doi.org/10.1192/bjp.105.441.979 Published online by Cambridge University Press

TABLE II

Constitution of Sample Paired for Age, Sex and Liver Damage

Age	Males		Females	
<40	2		2	(1 with moderate liver damage)
40–	0		6	
50–	2	(1 with moderate liver damage)	6	
60–	4	(1 with moderate liver damage)	6	
70–	1	(1 with moderate liver damage)	4	(1 with moderate liver damage)
80 and over	0		3	
	9	(3 with moderate liver damage)	27	(2 with moderate liver damage)

TABLE III

Comparison of Amount of Adrenal Lipoids in Schizophrenia and Other Mental Illness (Paired Sample)

	Adrenal Lipoids		
	Grade 1	Grade 2	Total
Schizophrenia	26	10	36
Other mental illness ..	16	20	36
Total..	42	30	72

$\chi^2=5\cdot714$. n=1. $\cdot02>P>\cdot01$.

to be significantly less in the schizophrenic group when compared with the group with other mental illness. Because of the relationship of adrenal lipoids with the presence or absence of hypertension shown in our previous paper, we compared the incidence of hypertension in the schizophrenic and other mental illness groups (see Table IV) and found that hypertension was not likely to be responsible for the differences in lipoid content in the two groups.

TABLE IV

Incidence of Hypertension in Schizophrenia and in Other Mental Illness (Paired Sample)

	Hypertensive	Non-Hypertensive	Total
Schizophrenia	8	28	36
Other mental illness ..	9	27	36
Total..	17	55	72

$\chi^2=\cdot083$. n=1. $\cdot8>P>\cdot7$.

In addition to the apparent relationship between schizophrenia and adrenal lipoids, it was noticed that liver damage also appeared to be present more often in cases with a relative deficiency of adrenal lipoids. This is shown in Tables V and VI. Here the schizophrenic and non-schizophrenic groups

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TABLE V

Schizophrenia

Comparison of Amount of Adrenal Lipoids and Liver Damage (All Cases)

	Adrenal Lipoids		
	Grade 1	Grade 2	Total
Liver damage	9	0	9
No liver damage	21	11	32
Total	30	11	41

P (by Fisher's exact method) = ·04.

TABLE VI

Other Mental Illness

Comparisons of Amount of Adrenal Lipoids and Liver Damage (All Cases)

	Adrenal Lipoids		
	Grade 1	Grade 2	Total
Liver damage	18	11	29
No liver damage	104	154	258
Total	122	165	287

$\chi^2 = 5 \cdot 050$. n=1. ·05>P>·02.

are treated separately and in both cases the difference is just significant at the level of P<·05. Moreover, liver damage was found more often in schizophrenic patients (see Table VII).

TABLE VII

Liver Damage in Schizophrenia and Other Mental Illness

	Liver Damage		
	Nil	Some	Total
Schizophrenia	32	9	41
Other mental illness	258	29	287
Total	290	38	328

$\chi^2 = 4 \cdot 915$. n=1. ·05>P>·02.

It was noted that the nature of the liver damage was extremely variable and included conditions such as fatty degeneration, cirrhosis and extensive metastases, and in all cases showing maximal liver destruction lipoids were completely absent. Owing to the differences in age and sex composition referred to earlier, it was decided to examine a second sample paired for age, sex and adrenal lipoids and compare the numbers of cases with liver damage in the schizophrenic and non-schizophrenic groups. The constitution of this sample is shown in Table VIII and the comparison of these two mental groups in Table IX. The difference was not significant. The nature of the liver damage and the cause of death in these cases included in the second sample is shown in Table X and it will be seen that there is no consistent cause of liver damage. It would appear, therefore, that the relative deficiency of adrenal lipoids seen in schizophrenia is more likely to be a determining factor in a higher incidence of liver damage in this disease than the reverse. If, in fact, there is a relationship between these two factors, it appears probable that their interdependence might

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TABLE VIII

Sample Paired for Age, Sex and Amount of Adrenal Lipoids

Age	Males	Females
<40	1 (1)	3 (1)
40–	2 (0)	6 (0)
50–	2 (0)	6 (2)
60–	4 (1)	6 (3)
70–	1 (1)	4 (2)
80 and over	0	3 (1)
	10 (3)	28 (9)

Figures in brackets represent the number of cases in each sample with excessive adrenal lipoids.

TABLE IX

Comparison of Liver Damage in Schizophrenia and Other Mental Illness (Paired Sample)

	No Liver Damage	Moderate or Severe Liver Damage	Total
Schizophrenia	29	9	38
Other mental illness	33	5	38
Total	62	14	76

$\chi^2 = 1 \cdot 329$ (using Yates' correction). n=1. $\cdot 3 > P > \cdot 2$.

TABLE X

Type of Liver Damage and Cause of Death in Cases with Liver Damage in the Paired Sample (see Table VIII)

Mental Diagnosis	Age	Sex	Type of Liver Damage	Cause of Death
Schizophrenia	43	M	Malignant metastases	Mediastinal sarcoma
Schizophrenia	49	M	Multilobular cirrhosis	Pulmonary tuberculosis
Schizophrenia	52	M	Multilobular cirrhosis	Pulmonary tuberculosis
Schizophrenia	60	M	Multilobular cirrhosis	Cirrhosis of liver
Schizophrenia	79	M	Fatty degeneration	Bronchopneumonia, pyelonephritis, diabetes
Schizophrenia	28	F	Fatty degeneration	Renal failure following insulin coma
Schizophrenia	33	F	Malignant metastases	Carcinomatosis, carcinoma breast
Schizophrenia	49	F	Fatty degeneration	Aspiration pneumonia
Schizophrenia	78	F	Cholangitis	Toxaemia due to pyaemia
G.P.I.	38	M	Early intralobular cirrhosis	Bronchopneumonia
Organic dementia	58	M	Fatty degeneration	Lateral sinus thrombosis
Depression	62	M	Malignant metastases	Bronchopneumonia, glandular sarcomatosis
Chronic mania	67	M	Obstructive jaundice	Carcinoma head of pancreas
Alcoholic psychosis	67	M	Cirrhosis (multilobular)	Coronary thrombosis

result in the establishment of a vicious circle. The complete absence of sudanophilic staining and birefringence in all cases where maximal destruction of liver cells was seen was very striking. However, as the latter were entirely unselected cases and the numbers were few, 10 in all, a detailed study was not carried out.

The schizophrenic cases were subdivided into paraphrenics and schizophrenics and examined in relation to their adrenal lipoids but no significant difference was found (see Table XI). The other mental illness group was also subdivided as in Table XII and no significant difference was found between the groups in the amount of lipoids present.

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TABLE XI

Comparison of Amount of Adrenal Lipoids in Schizophrenia and Paraphrenia

	Adrenal Lipoids Grade 1	Grade 2	Total
Schizophrenia	25	8	33
Paraphrenia	5	3	8
Total	30	11	41

$\chi^2=0{\cdot}854$ (using Yates' correction). n=1. ·5>P>·3.

TABLE XII

Comparison of Amount of Adrenal Lipoids in Various Types of Non-Schizophrenic Mental Illness

	Adrenal Lipoids Grade 1	Grade 2	Total
Paranoid psychosis	16	19	35
Manic-depressive psychosis	17	22	39
Cerebral arteriosclerosis ..	42	66	108
Others	47	58	105
	122	165	287

$\chi^2=·963$. n=3. ·9>P>·8.

DISCUSSION

The biochemical aspects of schizophrenia have been recently reviewed by Richter (2) and Smythies (3) and endocrine changes have been assessed by Sands (4). Deviations from normal have been found by many investigators but, apart from a wide range in variation as compared with normal, the findings have often been conflicting. In connection with ketosteroid excretion, Reiss (5) has emphasized the marked variation from day to day, which shows fluctuations amounting to 200 per cent. in schizophrenia. Our results show an apparent relationship between schizophrenia and adrenal lipoids, which would appear on histological grounds to be a relative deficiency of lipoids when compared with other mental diseases.

As a similar tendency was seen in cases of liver damage irrespective of the mental disease or the nature of the damage, the conclusion was reached that liver tissue may be more vulnerable to agents of disease when adrenal lipoids are deficient. This might also explain the greater numbers of diseased livers in schizophrenics than in other mental diseases, though here the numbers were too small to be conclusive. Factors which indicate a disturbance of adrenal steroids in liver diseases are the increased secretion of aldosterone in hepatic cirrhosis (6) and (7) and the low concentration of 17-ketosteroids in severe liver disease (8) and (9). On the basis of poor eosinophil response to epinephrine in patients with portal cirrhosis, Finestone and Shuman (10) concluded that there was inadequate adrenal function in this disease state. In a series of autopsies on cases of alcoholic cirrhosis, Lloyd and William (11) found decreased lipoids in the adrenal cortex. Our work confirms this finding whilst relating it to damaged liver tissue resulting from a variety of diseases, and suggesting a lowered resistance to agents of disease due to a defect in adrenal steroid metabolism.

Over the years, much work has been carried out on liver function in schizophrenia, often with conflicting results. Richter (12) in his review of the

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subject concludes that some impairment of liver function is commonly present in schizophrenics as a group but may be related to different enzyme systems being affected to different degrees and that this is probably not a primary factor in the aetiology of the disease. Following insulin coma therapy the prognosis of schizophrenia was found to be good when high urinary keto-steroids are reduced and maintained at a steady level as compared with those which show continuing fluctuations (13). In this connection, the formation of protein-steroid complexes by the liver (14) might possibly be a factor of importance in maintaining this steady level, especially as the conversion of adrenal steroid compounds into the 17-keto state is now generally considered to be a function of the liver (15).

One modern concept of schizophrenia postulated by Osmond and Smythies (16) and recently reviewed by Smythies (3) supposes the mental and biochemical changes to be the result of a toxic metabolite, a so-called M substance having mescaline-like qualities. It is thought that in certain predisposed individuals the production of M substance, which is probably an oxidative metabolite of adrenaline, possibly adrenochrome or closely related substance, is activated by stress and maintained by the stress thus produced. It seems possible that should such a metabolite interfere with normal steroid metabolism, then the adrenal glands would suffer first and the resistance of the liver to disease agents might be lowered, especially if protein-steroid complexes normally formed or stored in the liver were disturbed.

Summary

1. The histology of adrenal glands in schizophrenics was examined post mortem and absence or deficiency of adrenal lipoid staining was found to be significantly greater than in a mixed group of other mental diseases.

2. Cases with liver damage also showed a similar deficiency and this was found to be just significant.

3. The schizophrenic group contained more cases of liver damage than the control group but when paired for age, sex and adrenal lipoids the findings were not significant.

4. It was concluded that disturbance in adrenal steroid metabolism was often present in schizophrenia to a significant degree. That such disturbance might render the liver more vulnerable to agents of disease was suggested, but in this connection numbers were insufficient to be conclusive.

References

1. Beattie, M. K., and Heasman, M. A., *J. Path. Bact.*, 1958, **75**, 83.
2. Richter, D., *Schizophrenia*, 1957. Richter (ed.). London and New York. p. 53.
3. Smythies, J. R., *Lancet*, 1958, *i*, 308.
4. Sands, D. E., *Schizophrenia*, 1957. Richter (ed.). London and New York. p. 77.
5. Reiss, M., *International Record of Medicine*, 1953, **166**, 196.
6. Leutscher, J. A., and Johnson, B. B., *J. clin. Invest.*, 1950, **33**, 1441.
7. Chart, J. J., and Shipley, E. S., *ibid.*, 1953, **33**, 560.
8. Pincus, I. J., Rakoff, A. E., Cohn, E. M., and Tumen, H. J., *Gastroenterology*, 1951, **19**, 735.
9. Dohan, F. C., Richardson, E. M., Bluemle, L. W., and Gyorgy, P., *J. clin. Invest.*, 1952, **31**, 481.
10. Finestone, A. J., and Shuman, C. R., *Amer. J. clin. Path.*, 1952, **22**, 348.
11. Lloyd, C. W., and William, R. H., *Amer. J. Med.*, 1948, **4**, 315.
12. Richter, D., *Schizophrenia*, 1957. Richter (ed.). London and New York. p. 57.
13. Batt, J. C., Kay, W. W., Reiss, M., and Sands, D. E., *J. Ment. Sci.*, 1957, **103**, 240.
14. Sandberg, A. A., and Slaunwhite, W. R., *Recent Progress in Hormone Research*, 1957, **13**, 209.
15. Conn, J. W., Fajans, S. S., Louis, L. H., Seltzer, H. S., and Arbor, A., *J. Lab. clin. Med.*, 1954, **43**, 79.
16. Osmond, H., and Smythies, J. R., *J. Ment. Sci.*, 1952, **98**, 309.

https://doi.org/10.1192/bjp.105.441.979 Published online by Cambridge University Press