The Cholesterol Content of the Serum in Mental Diseases.

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WITHIN recent years a considerable amount of work has been done upon the bio-chemistry of cholesterol, and valuable information has been acquired which has thrown light upon the important part which this substance plays in numerous physiological and pathological states. It will be of value in connection with the results described in this paper to shortly review some of the more outstanding facts which have been discovered.

It has been known for some time that cholesterol is a constant constituent of every cell in the body, and that substances of closely allied chemical composition are widely distributed in plant tissues. In certain organs it is very abundant, for example, in the white matter of the central nervous system, where it is present to the extent of 10 *per cent.* of the dried substance, and in the cortical portion of the suprarenals. As a rule it is present in two forms: (1) free cholesterol, and (2) cholesterol combined with various fatty acids, *e.g.*, cholesterol oleate, palmitate, stearate, etc. The general term cholesterol-ester is applied to the latter form. In blood serum cholesterol is chiefly in the form of cholesterol-ester, only a small amount of free cholesterol being normally present. It is an important constituent of bile, in the form of free cholesterol, and the different forms in which cholesterol exists in the two fluids, serum and bile, should be noted, as this fact is of importance in the study of cholesterol metabolism. The work of Dorée, Gardner, and others (1) has suggested that in the metabolism of cholesterol there is a very definite circulation of a conservative nature, the free cholesterol of the bile being reabsorbed in the intestine, probably as cholesterol-esters, and carried by the blood stream to various tissues to be made use of in the building up of new cells. The changes which occur in cholesterol metabolism in various pathological states have been widely investigated (2). It has been found that the cholesterol content of the blood, bile, and suprarenals may vary within very wide limits. Normally, the total cholesterol (that is to say, both free and combined cholesterol) of the blood serum is from 1·5 to 1·8 grm. per litre, of the bile 1·5 to 1·6 grm. per litre. In pregnancy the content in

the blood may rise to 4·25 grm. per litre, and, associated with this, there is corresponding increase in the amount of free cholesterol in the bile. It has been suggested that the increased cholesterol content in the pregnant state is due to disturbance of the ovarian functions. An increase in blood cholesterol also occurs in cases of adiposity, diabetes mellitus, xanthoma, arteriosclerosis, chronic nephritis, eclampsia, and chronic jaundice. The amount of cholesterol in the bile in cases of gall-stone is unusually large, and the formation of gall-stones (which are frequently composed of almost pure cholesterol) is now regarded as a direct sequence of this increase.

Of the total cholesterin in the body the great bulk is, however, localised in the central nervous system, particularly in the white matter of the brain. The function of this very considerable amount of cholesterol is unknown. Lorrain Smith and Mair (3) found that in general paralysis there is practically no diminution of the amount of cholesterol, and that in the development of the brain the amount of cholesterol relative to other lipoids remains remarkably constant.

In cerebro-spinal fluid cholesterol may be found in many psychoses, both in the form of crystals and by means of the Liebermann colour test. In a recent paper Weston (4) describes the presence of cholesterol in the spinal fluids from a great variety of psychoses, the average amount of cholesterol in cases of epilepsy, dementia præcox, and organic dementia being greater than in general paralysis, senile dementia, and in manic-depressive psychoses. Crystals of cholesterol-esters, which are readily recognised by means of the polarising microscope, may also be found. In a case of optic atrophy examined by us the spinal fluid was distinctly turbid from the presence of such crystals.

It seemed to us that a systematic examination of the amount of cholesterol in the sera of cases of mental diseases might be of interest, particularly if the results were associated with observations on the cholesterol content of the suprarenals and the bile. For the estimation of cholesterol two methods are at present in general use. The first, which is extremely accurate, is the digitonin method of Windaus (5), and is employed where larger amounts of cholesterol can be obtained. This method depends on the fact that digitonin, a glucoside of the digitalis series, combines under suitable circumstances with cholesterol to form a stable crystalline compound, digitonin-

cholesteride. The amount of cholesterol present in this compound is constant and in the ratio of one part in four parts of digitonin-cholesteride. This method is the most convenient for the estimation of cholesterol in brain and other tissues. The second method, a colorimetric one, is suitable for the estimation of small amounts of cholesterol, and has been used by us in combination with a Könisberger-Autenrieth colorimeter. The method, as we have used it, is as follows: Blood to the amount of about 10 c.c. is drawn off from the median basilic vein and allowed to clot; the serum is separated; 1 c.c. of serum is pipetted off, placed in a small flask, 20 c.c. of 2 *per cent.* caustic soda added, and the flask heated on the water-bath for two hours. As a result of this treatment with caustic soda the cholesterol-esters are saponified, and the cholesterol separated as free cholesterol. The fluid in the flask is now transferred to a separating funnel and shaken for a period of two or three minutes with two to three times its volume of ether. The mixture is allowed to settle, the ether drawn off, and the fluid again shaken with a fresh amount of ether. The ether extracts are accumulated in an evaporating basin and the ether driven off on the water-bath. The residue in the basin is dissolved in 20 c.c. of chloroform. Five c.c. of this solution are carefully pipetted into a small test tube, and 2 c.c. of acetic anhydride and 0·1 c.c. of strong sulphuric acid are added. The tube is shaken to ensure thorough mixture and placed in a dark cupboard for twenty-five minutes. The depth of colour of the fluid is then compared with the standard coloured fluid in the colorimeter, and the amount of cholesterol calculated by reference to a curve which has previously been made by the use of known amounts of cholesterol in combination with the standard fluid of the colorimeter. This method in our hands has given very uniform results. The accuracy of the colorimetric method has been on occasion controlled by comparison of the findings with those obtained by the use of the digitonin method.

The estimation of the "free" cholesterol of the serum is carried out with another sample of the serum. One c.c. of the serum is diluted with 20 c.c. of water and extracted with ether. The procedure is then similar to that described above. The amount of "combined" or ester-cholesterol is obtained by subtracting the amount of "free" cholesterol from the total cholesterol.

The total number of sera examined was about 120. The accompanying tables give a sample of the kind of results which were obtained. Unfortunately it is not possible for us to give in detail the results of the examination of the whole 120 sera. Owing to a serious outbreak of fire in the laboratory at the institution, practically the whole of the records of this work, the colorimeter, and the stock of standard coloured fluid, were destroyed. The results shown in the tables were fortunately in another part of the laboratory, and are the only details of these experiments which escaped destruction. An examination of the tables shows that, on the whole, the cases of general paralysis had a very low cholesterol content and the cases of dementia præcox a content considerably higher than normal. The majority of the other cases gave figures which were slightly under normal limits. A few cases of chronic mania gave readings as low as some of the cases of general paralysis. In one case of mania, in which extreme excitement had continued for a period of seven months, there was a progressive fall in cholesterol from 1·8 grm. at the beginning of the attack to 0·2 grm. per litre at the end of the attack. All the epileptics gave practically normal readings. With the exception of early cases of dementia præcox there is, therefore, on the whole a distinct tendency in cases of prolonged mental disease for the cholesterol content of the serum to fall. The cases of general paralysis with one exception were in the second or third stage of the disease. In the exceptional case, in the first stage, the cholesterol content was 0·8 grm. per litre.

Attention has been drawn above to the fact that the cholesterol content of the suprarenals increases or decreases with the cholesterol of the blood. With regard to the increased cholesterol in cases of dementia præcox it should be noted that several observers have found that hypertrophy of the suprarenals frequently occurs in this disease.

Attention should also be drawn to the contrast which exists between the high cholesterol content of the serum reported in cases of chronic nephritis and arteriosclerosis, and the low content observed in our cases of general paralysis, a disease in which diffuse degenerative changes in the blood vessels are well marked. We have in all our cases endeavoured, as far as possible, to select for examination only

those cases which showed no pronounced renal or arterial changes.

We would suggest that a possible explanation of the above results may be found in the different degrees of activity of the sexual and reproductive tissues in the different psychoses. The high content of cholesterol in the dementia præcox cases would thus be an expression of an unusual degree of activity of the sexual glands, the low content of cholesterol in the advanced general paralytics an index of great loss of functional activity of the same organs.

It was our intention when this work was commenced to examine, in addition to the blood, the cholesterol content of suprarenals and bile. Owing, however, to the destruction of our material by fire, and to the interruption of research work by the war and the departure of Dr. Tisdall on military service, we have thought it advisable to put on record at the present time this preliminary note of the serum examinations alone.

TABLE I.

Case.	Mental disease.	Total cholesterol in grm. per litre of serum.
1	General paralysis	0·4
2	ditto	0·4
3	ditto	0·8
4	ditto	0·2
5	ditto	0·2
6	ditto	0·4
7	ditto	0·6
8	ditto	0·2
9	ditto	0·8
10	ditto	0·2
11	Dementia præcox	2·5
12	ditto	2·2
13	ditto	2·6
14	ditto	3·5
15	ditto	2·8
16	ditto	2·2
17	ditto	3·1
18	ditto	1·6
19	ditto	2·2
20	ditto	1·8

TABLE II.

Case.	Mental disease.	Total cholesterol in grm. per litre of serum.
21	Chronic melancholia	1·8
22	ditto	1·1
23	ditto	1·0
24	Agitated melancholia	2·1
25	Chronic mania	0·2
26	ditto	0·8
27	ditto (mild type)	1·1
28	Alcoholic insanity (chronic)	0·6
29	ditto (acute)	1·8
30	ditto (acute)	1·0
31	Epileptic insanity	1·3
32	ditto	1·4
33	ditto	1·2
34	ditto	1·5
35	Terminal dementia	1·0
36	ditto	0·3
37	ditto	1·1
38	Confusional insanity	1·0
39	ditto	1·1
40	ditto	2·1

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(5) Windaus.—*Ber. d. deutsch. chem. Gesellsch.*, 1909, Bd. xxxii, p. 254.

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