CHOLESTEROL: ITS RELATION TO MENTAL DISORDER.*

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During the last ten or twelve years a great deal of study has been devoted to cholesterol, its metabolism and variation in disease, and its rôle in mental disorder. Since 1926, investigations on this line, laboratory and clinical, have been carried out at Severalls Mental Hospital, and the object of the present paper is to summarize this research, especially in the light of other work, and to indicate what conclusions might be formed.

Cholesterol is a crystalline solid, insoluble in water, readily soluble in ether, acetone, chloroform and other organic solvents. Chemically it is a secondary alcohol containing one unsaturated bond, and capable of combining with organic acids to form esters. (All quantitative references to cholesterol in this paper are intended to indicate the total of free and ester cholesterol.) It is a constituent of all animal cells in free and combined forms, and similar sterols are present in all vegetable cells. The brain and spinal cord and the suprarenal glands contain a large proportion. In the blood it is distributed about equally between the erythrocytes and the plasma. Most of the research on cholesterol in relation to mental disorders has been carried out by observing changes in the blood cholesterol.

Undoubtedly the most accurate way of estimating the cholesterol content of the blood is the digitonin method, but the process is long and digitonin is expensive. For comparative purposes, if proper precautions are taken, the colorimetric method is suitable, and it is extensively adopted. The technique I have followed has been described elsewhere (1), and need here be only briefly summarized. Blood-serum is dried in plaster of Paris, which is then powdered, placed in a thimble, and extracted with hot chloroform for two or three hours in an all-glass extraction apparatus; the extract is concentrated, made up to a suitable volume, and compared with a standard solution in a colorimeter, by Liebermann's reaction; duplicate estimations are carried out on each serum, and the method is checked occasionally by making about fifteen estimations on a given serum, and calculating the probable error from a formula based on the method of least squares. The serum is obtained from venous blood, taken as far as possible under standard conditions. It is not advisable to use whole blood; indeed Gardner (2) has stated that it is essential to use plasma or serum to avoid complications due to anæmia, and on account of the masking of the dissolved cholesterol variations by the large quantity in the

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erythrocytes. It is important that the extraction apparatus should be all glass ; it is impossible to make accurate comparisons when the chloroform has come into contact with rubber. Care must also be taken in selecting a plaster of Paris which is free from impurities soluble in chloroform ; I have tried some brands which impart a yellow colour to the solvent, making comparison with a standard useless. Some biochemists extract the serum, plasma or whole blood after drying on filter-paper ; I gave this an extensive trial a few years ago, and found the results to be always lower than when plaster of Paris was used. I suspect that the high concentration of protein and salt crystals on a small piece of filter-paper prevents complete extraction. The method of extracting cholesterol from 10 c.c. or 20 c.c. of blood and attempting to weigh it can hardly be expected to give reliable results.

A precaution which is absolutely essential is the ascertainment, by each individual worker, of the limits of blood cholesterol in normal subjects. The normal figures found by others ought not to be used for comparative purposes.

The blood cholesterol changes in mental diseases have not been very widely studied ; and the results published, and the conclusions drawn from them, are very inconstant. This is partly due to the small numbers of cases considered, the difference in methods, and the failure in some cases to establish a normal standard ; but it seems probable that another reason mainly responsible is the classifying of results according to ill-defined diagnostic labels. This is clearly shown by the fact that there is little disagreement concerning the blood cholesterol variations in fairly well-defined entities, such as nephrosis, arterio-sclerosis, mental deficiency and senility, but much divergence of opinion when cases are considered under such headings as epilepsy, dementia præcox, mania and melancholia. The classification of results according to such diagnoses, without qualification, ignores two important facts : firstly, the impossibility of establishing with certainty a diagnosis which can be generally accepted—a difficulty well known with regard to the young manic-depressive and schizophrenic types ; and secondly, that the patient's metabolic variations, of which an altered blood cholesterol may be one, are influenced by his mental outlook, and particularly his mood—features which are not necessarily implied in the diagnosis entered in the hospital register. This criticism applies, of course, not only to blood cholesterol variations. The work of Cannon on blood sugar is well known, yet the blood sugar of psychotics is frequently discussed without regard to the fact that it may have been influenced by fear or rage. The visible bodily manifestations of anger and apprehension in the mentally deranged do not appear to differ qualitatively from those of the healthy individual, and one is justified in assuming, at least until there is some evidence to the contrary, that these mood changes will produce metabolic alterations which are likewise similar in the mentally normal and abnormal. It is, therefore, of the greatest importance that the exact mental state of the patient should be recorded when referring to blood cholesterol estimations or any clinical

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or biochemical examination; and if, for convenience, the results are tabulated under the recognized headings of psychiatric diagnosis, they should be further considered in relation to the mood changes.

The observations of other workers on the subject of blood cholesterol in the insane have included very few extensive series. C. J. and M. Parhon (3) examined 48 cases, using serum; in dementia præcox the figures were variable, but tended to be low in the chronic forms, and a diminution was also found in melancholia and in one imbecile; chronic alcoholism and senile states gave high results, and general paralytics showed nothing constant. Targowla, Badonnel and Berman (4) estimated the serum-cholesterol in 60 psychotics; it was found to be raised in chronic alcoholism, early general paralysis and agitated melancholia, and diminished in mental deficiency and epileptic confusion. In confusional states and in epileptics the figures were variable, but tended to be high. The French school has always emphasized the possibility of an association between blood cholesterol and the sympathetic-endocrine system. Hypercholesterinæmia was found almost constantly in 36 senile patients by Tinel, Dupouy and Schiff (5), and in 52 out of 66 chronic alcoholics by Ducceschi (6). In special epileptic investigations the published results have shown much disagreement. Jacobi (7), who examined 23 cases, considered that the blood cholesterol is high, and increases further after a fit. Gray and McGee (8) tested 623 epileptics, using whole blood; the average figure was 165, compared with a normal average of 194; one hour after a fit the average was 162. Robinson, Brain and Kay (9) also found low results in epileptics, especially within twenty-four hours of a fit; they believed that the pre-convulsive period coincided with a diminution. Goodall (10) could find no appreciable difference as the result of fits; Malerba (11) found low serum cholesterol in epileptics. Goebel (12) considered an increase to occur before a fit. He also found the figure to be high as a rule in dementia præcox, and sometimes in general paralysis and cerebral syphilis. Jacobi's (7) other investigations included 19 cases of dementia præcox, with inconstant results, and 20 cases of manic-depressive insanity, the majority showing hypercholesterinæmia. Gibbs (13) obtained low figures in 38 primary dements, especially when associated with recent acute mental states. Forsyth (14) also considered dementia præcox cases to have a lower blood cholesterol than other psychotics. Stenberg (15), on the other hand, found high figures in early dementia præcox, and normal results in the few remissions examined; he considered that emotional states are accompanied by a rise in blood cholesterol, while apathy is associated with a diminution; this variation was shown by 7 manic-depressive cases examined during remissions as well as when mentally ill. Lockwood (16) obtained inconclusive results in a group of 24 manic-depressives, but observed the interesting fact that blood cholesterol varies inversely with the hyperglycæmic index. Gray and McGee (8) also examined 108 mental defectives, and found hypocholesterinæmia predominating. In a series of neuro-syphilitics the results

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of Rosen, Krasnow and Notkin (17) were inconstant, but McFarland (18) found a large proportion of high serum cholesterols in similar cases. Schube (19) examined 200 cases of mental disorder, and comparing them with a normal series, found a greater range of blood-cholesterol figures, 52% being below the normal limits, but the figures are not given for the actual types of disorder. Shaw and Sharpe (20) found marked hypocholesterinæmia in 10 cases of primary dementia, and an abnormal increase in states of mania.

My own series of 336 cases has already been published (1), but I must briefly summarize it here, since the results have considerable bearing on the further investigations. The serum cholesterol is high in cases of dementia præcox showing emotional indifference, and within normal limits in those characterized by confusion or emotional excess; when a dull patient becomes excited or agitated, his serum-cholesterol is much lower. In mood psychoses also the cholesterol content is high during remissions, when the emotional state approximates to normal, and falls with a relapse into a manic or melancholic state. Chronic alcoholism shows similar changes. In epilepsy the figure is again high, and a reduction occurs with periods of confusion, and often in association with a fit. Imbeciles without complications have practically normal cholesterol values; imbeciles with epilepsy or prominent mood changes show the cholesterol variations of these disorders. The usually high serum cholesterol of organic dementia and senile states need not be further considered.

Briefly, an increase in emotional tone is practically always associated with a fall in the blood cholesterol, whether the initial value is high or within normal limits, and whatever the type of mental disorder. It seems very probable—though this would be difficult to verify—that a similar reaction occurs in the mood variations of the healthy individual. Whether this be so or not, one is naturally led into a consideration of how an alteration in the blood cholesterol could be associated with emotion, the mechanism by which one might be induced by the other, and the biological value of the reduced cholesterol content.

The association between emotion and the endocrine glands is well recognized; the influence of the latter on the blood cholesterol has been stressed by the French workers, but has attracted little attention in this country. Most work has been done in relation to the thyroid gland, observations being made on patients with thyroid disease, on animals after thyroidectomy, and in association with thyroid administration. Luden (21), in 1918, observed the blood cholesterol to be high in myxœdema, with a return to normal after appropriate treatment, and within the normal range in Graves's disease. In 1924, Epstein and Lande (22) found the blood cholesterol to be lower than normal in exophthalmic goitre, and high in cases of subnormal basal metabolism, in which they included myxœdema and chronic nephritis. Gardner and Gainsborough (23) criticized these findings, and denied any association between basal metabolism and cholesterol; they did, however, find the plasma content in 14 cases of hyperthyroidism to be a little lower than normal, and

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agreed that the value is high in untreated myxœdema. Rémond, Colombies and Bernardbeig (24), in 1924, found hypercholesterinæmia in rabbits after thyroidectomy and parathyroidectomy. Since the observations of the earlier workers many records have been published demonstrating the effect of thyroid on the blood-cholesterol. In patients with thyroid disease there are the findings of Wade (25), Laroche (26), Mason, Hunt and Hurxthal (27), Max Lévy and M. E. Lévy (28); in animals the experiments of Wade (25), Blinoff (29), Parhon and Derevici (30), Onizawa (31), and Westra and Kunde (32); some of these have also tested the effect of thyroid administration. There is almost complete agreement in the conclusions, and it may be accepted that the administration of thyroid extract lowers the blood cholesterol; pathological or experimental deprivation of the gland increases it; and the tendency is for Graves's disease to be associated with a lowered content, though not necessarily below the normal limits.

In 1928, while treating with thyroid extract a patient with dementia præcox whose appearance suggested subthyroidism, I recorded a fall in serum cholesterol from 502 to 158 mgrm. per 100 c.c.; coincident with this there was a great improvement in the mental state. Relapse into an apathetic condition and a cholesterol rise to 414 followed suspension of treatment. To test the effect of administration of the gland to psychotic patients a number of different types were treated for varying lengths of time, and the serum cholesterol estimated at brief intervals. The 22 patients thus investigated included ten different types of mental disorder, "functional" and organic; the details have been recorded elsewhere (33). In every case the result was the same. The effect of thyroid administration is a rapid fall in the cholesterol content of the blood; with a constant dose the diminution presently becomes more gradual, or there may be a tendency to increase, which may even be maintained on large doses. The result of stopping thyroid is always an increase in the blood cholesterol, often to an amount considerably in excess of that recorded before treatment. The variety of cases dealt with makes it obvious that the effect of administering the gland is not in any way associated with any special psychosis, and strongly suggests that it would occur in those without mental disorder. The results are thus consistent with those of Luden, Epstein and Lande, and others referred to above The tendency of blood cholesterol to rise in spite of persistent thyroid administration also explains the failure of Gardner and Gainsborough, and others, to find hypocholesterinæmia in Graves's disease.

Comparing the results of this investigation with the former record of blood cholesterol in the insane, it is seen that there is a striking similarity of the thyroid reduction of cholesterol to that accompanying excessive emotion. This parallelism makes it possible to explain the cholesterol changes in psychotics. The thyroid gland is part of the mechanism concerned with the bodily reaction to an emergency, including the emotional changes of this reaction. The raised blood cholesterol of the emotional deterioration typically

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seen in some primary dements is, therefore, to be associated with the similar picture found in myxœdema and in animals after thyroidectomy. Temporary excessive emotion, such as excitement or agitation, like temporary feeding with thyroid, lowers the blood cholesterol, and subsequently there is a rise to a higher level than before ; this explains the hypercholesterinæmia of remissions following acute mental states, the cessation of emotional stimulation of the gland being similar to cessation of thyroid administration. Finally, the tendency of the blood cholesterol to rise after its initial fall, even while thyroid extract is continued, is consistent with the raised level found in prolonged states of mania and melancholia. It is probable that emotion causes a lowering of blood cholesterol by stimulation of the thyroid gland.

Can this be correlated with the other known functions of thyroid secretion and with what is known of the part played by cholesterol in metabolic activity ? G. W. Henry (34) has carried out an interesting investigation of the basal metabolic rate in mental disorders, and has found that excessive emotion and increased psycho-motor activity are associated with accelerated basal metabolism ; apathy and retardation are characterized by slowing of the basal metabolic rate. The function of the thyroid in stimulating metabolism is well recognized. How this influence is exercised, whether directly on the tissue-cells or by way of nervous stimulation, is unknown ; it is worth while considering whether an alteration of the cholesterol in the blood and tissues can be concerned in this function. In doing so it is necessary to refer briefly to the other known variations of this substance in the body, and to its biophysical properties.

With regard to metabolism, the situation has been summed up by Gardner (35). " We know nothing whatever of the function of cholesterol in the cell, and very little of the part it plays in general metabolism." The physiological and morbid variations of blood cholesterol have been recorded by Gardner (35), Chamberlain (36, 37) and others. Gainsborough (38) observes that the level can be raised or lowered by prolonged feeding with diets rich or poor in cholesterol, but hypercholesterinæmia cannot be induced as the result of a single meal. The only alteration which seems to be connected with the subject here considered is the hypocholesterinæmia of fever, the reasons for which, Gainsborough states, are not understood. Diminished blood cholesterol is noted by Campbell (39) as occurring in most acute infections, by Malerba (11) in acute febrile diseases, and by Gerard and Lemoine and others (41) in tuberculosis ; the cholesterol diminution during bacterial infections is stated by Chamberlain (40) to be proportionate to the intensity of infection. Lereboullet, David and Donato (42) made numerous tests on children suffering from diphtheria, and found rapid lowering of the blood cholesterol, especially in severe cases ; they note that intercurrent disorders, such as broncho-pneumonia and otitis media, always cause hypocholesterinæmia.

We have thus three types of case in which there is altered metabolic rate and variation in blood cholesterol—the emotional group, the thyroidic, and the

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pyrexial. Are there any biophysical properties of cholesterol which enable us to link the two associated conditions?

It is well known that lecithin and cholesterol are in some respects antagonistic. Burns (43), in his *Introduction to Biophysics*, states that the ratio of water to solids in a cell depends directly on the cholesterol content and indirectly on the lecithin content. He quotes Leathes, who showed that when a molecular layer of lecithin is spread on water, the area covered is reduced by cholesterol: "In some way this alcohol causes the long-chained phospholipin to pack its molecules more closely together". Mathews (44) notes the protective action of cholesterol against hæmolysis of red cells, and its neutralizing or retarding action against some lipolytic enzymes. The experiments of Shaw and Sharpe (20) in the laboratory of the County Mental Hospital, Stafford, are of great interest. Using washed erythrocytes of sheep's blood and diluted cobra venom, they showed that the presence of lecithin caused the red cells, normally resistant to the venom, to hæmolyse, and that cholesterol, if added in an amount above a certain definite proportion to the lecithin, prevented or delayed hæmolysis. Their other experiments demonstrated the influence of cholesterol as a controlling factor in oxidative processes, and in reducing surface tension, especially in colloidal state; also its retarding action on the diffusion of potassium salts through a membrane. Tsuneyoshi's experiments showed the accelerating effect of lecithin and the retarding effect of cholesterol on the consumption of oxygen by tissue powder and on the oxidation of an amino-acid on charcoal (45).

Applying the knowledge of these physical properties to animal cells, it would appear that the greater the amount of cholesterol present, especially in proportion to lecithin, the lower will be the metabolic activity of the cells. This has been tested by investigations on the lecithin and cholesterol contents of normal and malignant tissue. Jowett (46) reasoned from the properties of cholesterol that cells having high metabolic rates, *e.g.*, growing or active cells, would show a low cholesterol-lecithin ratio so as not only to have more permeable membranes for the taking in of oxygen and nourishment from their environment, but to allow also more freedom for chemical activity between different parts of the cell. He analysed human tissues, normal and malignant, and obtained results tending to confirm that malignant cells have a low cholesterol-lecithin ratio. Jowett's results are consistent with those of Bennett (47), who, in 1914, found that the cholesterol content of cancerous tissue increases with the age of the tumour. Iwano (48) observed that the cholesterol content of the central part of a new growth, where activity is least, is higher than at the periphery, the lecithin percentage being constant. This was confirmed recently by Uramato (49), who made an extensive analysis of rat carcinoma tissue. He found that the cholesterol amount increases steadily with the age of the tumour, this increase being specially noticeable at the central portion of the growth in its later stages; lecithin, on the other hand, is present in the same percentage

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at the centre and periphery, and decreases equally in these regions with the tumour age. Evidently the cholesterol-lecithin ratio is lowest at the most active part of a carcinoma, and at its most active stage. Uramato also considers that oxygen consumption decreases with tumour age, but there does not appear to be any investigation into this point.

We have now sufficient evidence to associate, causally, a diminished blood cholesterol with increased metabolic activity of the tissue cells. It is hardly possible that neurons can escape sharing in this association, and we can attempt to link up the blood cholesterol variations dependent on thyroid secretion or emotion with nervous activity, and so with mental disorder; but caution is necessary in reasoning from a variation of physiological activity, such as altered metabolic rate, to a pathological condition of nerve-cells. It is highly improbable that alteration in blood cholesterol, which is subject to physiological variations—including those of emotion—could in any way lead to disease or death of nerve-cells; I can no more imagine neuronic decay resulting directly from moderately high or low blood cholesterol than from moderately high or low blood sugar. The neuron will therefore be considered here as being affected only as it has been shown that any other cell might be affected—that is, in increase or decrease of its own activity. On this basis a diminished blood cholesterol will tend to produce increased neuronic excitability and activity, with increased psychomotor activity and probably emotional manifestation; a raised blood cholesterol should diminish nervous activity and cause mental retardation and apathy. The association between the nervous system and cholesterol is thus a reciprocal one; excitement lowers the blood cholesterol content, and a lowered blood cholesterol tends to increased nervous and mental activity. There must, of course, be limiting factors to prevent the establishment of a vicious circle with ever-increasing excitement and constantly falling blood cholesterol; the tendency already observed, for the blood cholesterol to rise after the preliminary fall, in spite of maintained thyroid administration, is one such restraining influence. There are probably others, dependent on the capacity of the reticulo-endothelial system, or whichever organs are so concerned, in taking up cholesterol from the blood.

The hypothesis so formed has some bearing on the treatment of abnormal mental states. If excess of cholesterol leads to diminished activity of the nervous system, states of apathy and retardation should respond favourably to any means of lowering the blood cholesterol content; and psychomotor over-activity might be improved by raising the value. It must, however, be emphasized that any such treatment can only be symptomatic; it could only be expected to give successful results when the condition is purely one of altered rate of nervous activity; a case of dementia præcox might be made less apathetic by stimulating the nervous system, but the delusions could hardly be affected, except in an adverse way. Mental hospital treatment, however, is so largely symptomatic that induced cholesterol variation is worth considering.

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(1) *Reduction of blood-cholesterol.*—The ideal case for such treatment is one of simple mental inertia, characterized by slow perception, retardation and apathy. Myxœdema provides the only example of such mental disorder, and one need not stress the necessity for thyroid administration. Mental improvement is coincident with the fall in blood cholesterol, and the thesis here advanced suggests that the improvement is directly dependent on such reduction. In other mental disorders the effects of diminishing the blood cholesterol are those which might be expected as the result of increased nervous activity. This was observed in the 22 cases previously mentioned in this paper, treated for varying periods with thyroid gland. The primary dements were stimulated to become less dull, more hostile, or even hypomanic. A melancholic showed increased agitation; the general paralytics became irritable and difficult to nurse. In the case of Parkinson's disease the tremor became more pronounced; the patient with simple mania remained manic until after thyroid treatment was stopped, when a marked improvement coincided with the rise in blood cholesterol to a high level.

In some cases of dementia præcox another beneficial agent which probably acts by cholesterol reduction is fever, which has already been noted as lowering the blood cholesterol. It is not infrequently observed that such patients show improvement, often to a considerable degree, during and immediately after an acute febrile illness, and it is the dull and retarded patient who shows this best; the lowering of blood cholesterol has allowed the neurons to function more freely. With the subsequent rise to the former high level there is the almost inevitable relapse.

(2) *Raising of blood cholesterol.*—I have attempted this in cases of excitement and over-activity. On theoretical grounds the patient most likely to benefit is the one showing excessive emotion and increased psychomotor activity, uncomplicated by delusions or hallucinations. Simple mania often falls within these limitations, but the excitement of other mental disorders might be lessened by a substance which, if the conclusions here reached are correct, is a natural sedative. It is not easy to raise the blood cholesterol content; the mechanism maintaining it at more or less constant level seems to act more readily in removing excess than in supplying deficiency. As Gardner pointed out, administration in the diet is only slowly effective, and I have had difficulty in getting patients to swallow the unpalatable emulsion of cholesterol in milk. Inunction with lanolin, which is largely cholesterol and its esters, has been tried in some of my cases, but too few to judge the effect; absorption is probably too slow, and removal from the blood too rapid, for a successful result. Leopold and Bernhard (50), however, have reported that the blood cholesterol of children can be raised by lanolin inunction followed by ultra-violet radiation; and they quote Berman as having obtained a similar effect. The most rapid method of producing hypercholesterinæmia is intramuscular injection of cholesterol dissolved in

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olive oil. Harris and Lipkin (51), during some experiments on blood-pressure, found a considerable rise in blood cholesterol one hour after injection of 1·5 grm., with return to normal within a few hours. I have tried injections in 24 patients, some of them on repeated occasions in different relapses. Four cases may be quoted as illustrating the results:

(1) *Acute confusion.*—A man, æt. 55. Excitable, resistive, restless, sleepless; duration six days. Cholesterol in 1·0 grm. doses, intramuscular, on January 18, 20, 22 and 25, 1931. Temporary improvement was apparent within four hours after each of the first three doses; excitement diminished and he was able to sleep; six hours after the third dose he was mentally clear and conversed rationally. The fourth dose was given after a few hours' further restlessness, and was followed by drowsiness. There was no further excitement; he was ultimately discharged, though recovery was incomplete, there being periods of depression.

(2) *Epileptic confusion.*—Male, æt. 50. Excitable, restless and confused for nine days. One-gramme doses on November 28 and 30, 1930. Drowsiness for two days after second dose, then rapid recovery. No relapses occurred and he was discharged as recovered.

(3) *Dementia præcox.*—A man, æt. 28. Duration two months; katatonic excitement for eight days. Two injections of 1·0 grm. with an interval of forty-eight hours. Improvement within six hours of the first dose; a few hours after the second he became stuporose, and remained more or less so, without any excitement, for about a month; improvement then followed and he was discharged seven months later.

(4) *Recurrent mania.*—Fourth attack; male, æt. 55. Duration twelve days. Typical manic condition. Two injections of cholesterol, with a two-day interval; improvement twenty-four hours after the first dose, and recovery was uninterrupted.

The whole 24 cases may be summarized briefly. In 13 patients injection of cholesterol seemed to be effective in reducing excitement within a few hours, Indications of relapse one to three days later were frequent, but further improvement occurred shortly after second or third doses, often with rapid recovery from the acute state, occasionally only gradual. Five of these 13 were chronic relapsing patients, and the treatment did not appear to prevent later relapses, but in three cases these have been much less frequent in the two and a half years since treatment. Of the 8 recent cases, 5 were discharged and 3 became chronic mental invalids. The 11 cases in which cholesterol injections had no immediate effect included 3 epileptics, 1 involution manic state, 1 case of agitated melancholia, and 6 cases of excitement in the course of dementia præcox.

The cholesterol solution was prepared by dissolving 1·0 grm. in 20 c.c. olive oil in long-necked bottles, which were then sealed and sterilized in boiling water for an hour on three successive days. When cold, this amount of cholesterol is not completely soluble, but easily dissolves on heating. The warm solution was injected into the gluteal muscles. The maximum dose used was 1·5 grm. but 1·0 grm. was the usual, and sometimes 0·5 grm. on successive days. No ill-effects were observed, apart from slight transient pyrexia in 2 cases, and in 1 case a rapid pulse for two days. To exclude the possibility of the olive oil having any effect, a frequently relapsing patient, in whom cholesterol injections

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were followed by a remission, was given, during the next relapse, two injections of pure olive oil; the excitement was not influenced, but when seventeen days later cholesterol in oil was used for the third injection, there was temporary improvement.

Definite conclusions must not be drawn from the results of cholesterol injection; the cases tried are too few, and the state of increased psychomotor activity which was considered an indication for the treatment is one in which rapid and spontaneous improvement is frequent; but the often observed sedative effect within a few hours of the injection, when the increased blood cholesterol was probably at a maximum, suggests that in some cases the change is due to the cholesterol, and this view is at least consistent with the suggested association between blood cholesterol and mental state.

Possibly connected with induced hypercholesterinæmia is the method of treatment which has been suggested for persistent melancholia after return of good bodily health—that of making the patient physically ill by thyroid administration for a week. Stoddart (52) recommends increasing doses up to twelve 5-gr. tablets daily, and states that the patient usually deteriorates physically and mentally under this treatment, but that subsequent improvement and recovery occur in a number of cases. This may be due to the considerable rise in blood cholesterol which follows the cessation of thyroid feeding.

Summary.

The facts which have been considered, and the conclusions which seem justified from them, may be summarized as follows:

(1) Blood cholesterol is lowered in certain general conditions affecting the organism as a whole: (*a*) Heightened emotion and quickened psychomotor activity; (*b*) fever; (*c*) hyperthyroidism. A factor common to all these is increased metabolic rate.

(2) Blood cholesterol is raised in (*a*) apathy and diminished psychomotor activity; (*b*) subthyroidism. In each of these conditions there is diminished metabolic rate.

(3) The properties of cholesterol are such that when the cholesterol in blood and tissues is lowered, increase of metabolic rate is to be expected; when cholesterol is increased, diminished metabolism should result. The analysis of actively-growing tissue supports this view.

(4) Therapeutically induced diminution of blood cholesterol acts on the nervous system, in some cases at least, as a stimulant, causing increased mental activity.

(5) Therapeutic raising of the blood cholesterol acts on the nervous system, in some cases, as a sedative, causing diminished mental activity.

It is concluded that cholesterol is one of the controlling factors of cellular metabolism, and that neurons are susceptible to quantitative changes of this substance in their environment.

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Although this conclusion fits in with the observed facts, and even if it be confirmed by further research, it must not be considered that it settles more than one aspect of the relationship of cholesterol to neuronic function and mental disorder. Obviously there are many agents by which the rate of activity of the nerve-cell may be influenced, some of them probably closely related to cholesterol; lecithin, for example, must be an important factor. Although the studies here recorded have dealt with cholesterol alone, it has not been forgotten that the functions of this substance can hardly be isolated from those of many others; the hypothesis formed is but a working basis—I think an accurate one—for further investigations. It must be emphasized that no attempt is made to associate cholesterol with pathological conditions of the nervous system, or with such diseases of the mind as lead to altered personality. The association is strictly confined to those disorders and symptoms which can be regarded as physiological activities altered only in degree. The therapeutic indications arising out of the conclusions must also be regarded with caution until the influence of other associated factors is more fully understood. Finally, if it be argued that so much is excluded, and so little of practical value remains, it can be pleaded that there is indicated the direction in which future investigations can profitably be made, and even if such research should add little to psychiatric knowledge, there is the probability that it would throw light on a very obscure corner of physiology.

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