THE SIGNIFICANCE OF CHOLESTEROL IN CELLULAR OXIDATION AND ITS BEARING ON MENTAL DISORDER.

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Sterols, such as cholesterol, phytosterol, etc., are present in all animal and vegetable tissues, and play a most important *rôle* in physiological and pathological processes. For example, it is well known that cholesterol has a powerful influence in aiding complement fixation in sero-diagnosis—it checks the action of lipolytic enzymes and inhibits the hæmolytic action of saponins and cobra venom on erythrocytes. It is an important factor in giving cells their power of holding large quantities of water without losing their peculiar semi-fluid characters and without dissolving. Citron (1) states that '1 c.c. of an emulsion of central nervous system neutralizes three times the fatal dose for mice of botulism toxin and that lecithin and cholesterol act similarly.

A *résumé* of certain investigations respecting the significance of cholesterol and lecithin in metabolism will now be given and the results considered.

(1) Experimental Evidence of the Influence of Cholesterol on Ferment Action and Oxidation Processes.

Certain washed erythrocytes are hæmolysed by cobra venom and others are not. This appears to be dependent on the proportion of cholesterol to lecithin in these corpuscles. For example, the red corpuscles of the rabbit are readily hæmolysed by cobra venom, and the percentages of cholesterol and lecithin in them are ·072 and ·490 respectively, while the corresponding percentages in the case of the sheep, whose corpuscles are entirely resistant, are ·380 and ·410 respectively. The hæmolytic power of cobra venom

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is considered to depend on the presence of an enzyme which has the remarkable property of acting on lecithin by hydrolysing its unsaturated fatty acid groups. Levene has suggested the name of "lysolecithin" for this compound. This lysolecithin has powerful hæmolytic properties, but it also has a marked affinity for cholesterol, and the loose compound resulting is devoid of hæmolytic properties. The following table of results, using washed sheep's corpuscles, illustrates the effect of lecithin in facilitating hæmolysis and the inhibiting action of cholesterol :

Venom 1/5000 in N.S. . .	1 c.c.	1 c.c.	1 c.c.	1 c.c.	1 c.c.
Sheep's corpuscles, 4% in N.S. .	·5 ,,	·5 ,,	·5 ,,	·5 ,,	·5 ,,
N.S.	·5 ,,	·25 ,,	..	..	..
2% lecithin in N.S. . . .	..	·25 ,,	·25 c.c.	·25 c.c.	·25 c.c.
·4% cholesterol in abs. alcohol .					
1 in 5 N.S.	..	..	·25 ,,	..	..
1 in 10 N.S. . . .	..	..	..	·25 c.c.	..
1 in 20 N.S. . . .	..	..	..	..	·25 c.c.
	N.H.	C.H. in 10 min.	C.H. in 50 min.	C.H. in 25 min.	C.H. in 14 min.

N.H. = no hæmolysis; C.H. = complete hæmolysis; N.S. = normal saline.

In order to prevent the hæmolytic effect of the venom ferment, it is therefore necessary that cholesterol shall be present above a definite amount in proportion to the lecithin present.

The influence of cholesterol on the oxidation of lecithin will now be considered. Cholesterol and lecithin alone, and certain mixtures of them in definite proportions, were subjected to the action of potassium permanganate solution for varying lengths of time. The quantities were all dissolved in 5 c.c. CCl_4, and 50 c.c. of a standard permanganate solution added to each. The quantity of oxygen absorbed was found by the well-known iodine and thiosulphate method. During the time of action the mixtures were kept in the dark and frequently shaken. The results are as shown in the next table.

It will be seen that the amount of oxygen absorbed by cholesterol (columns 2 and 3) is negligible, while that absorbed by lecithin (columns 4 and 5) is very considerable. Comparing columns 4 and 6, it will be noted that the addition of cholesterol to lecithin in equal amounts inhibits the power of oxygen absorption by lecithin to the extent of 75%, and from columns 4 and 8 it will be noted that one part of cholesterol almost entirely inhibits the absorption of oxygen by three parts of lecithin. ·05 grm. of lecithin alone absorbing

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
Material.	Control $KMnO_4$ solution.	Cholesterol.	Cholesterol.	Lecithin.	Lecithin.	Cholesterol and lecithin.	Cholesterol and lecithin.	Cholesterol and lecithin.	Cholesterol and lecithin.	Cholesterol and lecithin.	Cholesterol and lecithin.
Quantity of cholesterol and lecithin (grm.)	..	·05	·05	..	..	·05	·05	·05	·05	·05	·05
	..	..	..	·05	·05	·05	·10	·20	·05	·10	·15
c.c. N/10 sodium thiosulphate used	32	32	31·8	26·2	19·1	30·4	29·9	26·5	19·5	27·0	24·3
Oxygen absorbed (mgrm.)	*Nil*	*Nil*	·14	5·08	11·2	1·4	1·84	5·12	2·5	4·31	7·0
Time	2 hrs.	2 hrs.	5 dys.	2 hrs.	30 hrs.	2 hrs.	2 hrs.	2 hrs.	24 hrs.	24 hrs.	24 hrs.

practically the same amount of oxygen as does ·20 grm. when associated with ·05 grm. cholesterol. Other considerations are also evidenced, *e.g.*, comparing columns 4 and 9, the inhibition exercised by cholesterol is obviously both powerful and prolonged.

Reverting to the relation of cholesterol to enzyme activity, it is noteworthy that when fresh human serum is added to cobra venom hæmolysis of sheep corpuscles is effected, but when the serum is inactivated at 56° for 30 minutes hæmolysis does not take place. This thermolabile substance present bears no relation to complement—in fact it seems to vary indirectly to it in a given serum. It would appear to vary directly with blood cholesterol, since in cases of recurrent mania with excess of cholesterol it tends to be more active than in cases of dementia præcox containing less than normal. In other words, it would seem to be an attempt on the part of the organism to counteract the disproportion of cholesterol to lecithin. When the latter is in relative excess this thermolabile substance diminishes, and contrariwise when cholesterol is in excess. The following is an example :

1/5000 venom in N.S.	1 c.c.	1 c.c.
3% sheep corpuscles	·5 ,,	·5 ,,
N.S.	·2 ,,	·2 ,,
Fresh patient's serum :		
Case of dementia præcox	·3 ,,	..
,, recurrent mania	..	·3 c.c.
	C.H. in 10 minutes	C.H. in 4½ minutes.

C.H. = complete hæmolysis.

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This is evidence of an attempt on the part of the organism to accelerate ferment action in order to counterbalance the inhibiting effect of excess of cholesterol on oxidation processes.

The Influence of Lecithin and Cholesterol on Surface Tension and Diffusion of Certain Ions.

By adaptation of the torsion balance, *viz.*, the suspension of a platinum ring on the surface of the fluid by means of a thread and estimation of the pull in milligrammes necessary to make the ring part company with the fluid, a simple and accurate method of estimating surface tension was devised. 50 c.c. of a 1% solution of glucose in distilled water to which 1 c.c. of alcohol had been added gave a reading of 384 mgrm. Subtracting 115 mgrm. from this—the weight of the platinum ring and thread—the pull exercised by the surface tension amounted to 269 mgrm. A similar amount of the glucose solution, to which 1 c.c. of an alcoholic solution of cholesterol was added, resulting in a colloidal cholesterol suspension containing ·1% of cholesterol, showed a reading of 340 mgrm., *viz.*, a pull of 225 mgrm. The addition of the cholesterol, therefore, caused a lowering of the surface tension by 44 mgrm.

It is of importance to note that cholesterol, when present in colloidal suspension, causes a much greater alteration in surface tension than when it exists in solution. Thus the surface tension of olive oil shows a reading of 102, and the addition of ·5% cholesterol only reduces it to 100, and 1% to 95. Since substances which lower surface tension tend to accumulate at the periphery, cholesterol will be in strongest concentration in and about the cell walls, and therefore exercises considerable effect on cellular metabolism so far as diffusion, nutrition and protection from extrinsic toxins are concerned.

The following tables illustrate clearly the effect of lecithin and cholesterol on the diffusion of K and Na ions. Tables A, B and C show the results of diffusion experiments using sodium and potassium salts as the crystalloid, with lecithin (brain extract, alcoholic, dried) as the colloid. Table C gives the results of experiments using a membrane impregnated with cholesterol.

DIFFUSION EXPERIMENTS: COLLODION MEMBRANES; 36 HOURS' DURATION.

TABLE A.—*The Effect of Lecithin on Mixtures of Na and K Salts. 1% Colloidal Lecithin in Distilled Water.*

	1.	2.	3.	Control.
Within membrane:				
Distilled water	10 c.c.	10 c.c.	10 c.c.	10 c.c.
Na_2CO_3	50 mgrm.	25 mgrm.	10 mgrm.	25 mgrm.
K_2CO_3	50 ,,	25 ,,	10 ,,	25 ,,
Lecithin	50 ,,	50 ,,	50 ,,	..
Outside membrane:				
Distilled water	30 c.c.	30 c.c.	30 c.c.	30 c.c.
After dialysis: Solution left outside membrane:	22 ,,	23·2 ,,	22 ,,	25 ,,
Water absorbed	8 ,,	6·8 ,,	8 ,,	5 ,,
Total solids dialysed	45%	50%	50%	60%
K_2CO_3 dialysed	16·3%	10%	11%	21·4%
Na_2CO_3 dialysed	28·7%	40%	39%	38·6%
Ratio K to Na.	1 : 1·76	1 : 4	1 : 3·6	1 : 1·8

TABLE B.—*The Effect of Brain Extract Within the Membrane on K Salts Outside Membrane.*

	1.	2.	3.	Control.
Within membrane:				
Brain extract	2 grm.	·1 grm.	·05 grm.	..
Distilled water	10 c.c.	10 c.c.	10 c.c.	10 c.c.
Outside membrane:				
KCl	50 mgrm.	50 mgrm.	50 mgrm.	50 mgrm.
Distilled water	30 c.c.	30 c.c.	30 c.c.	30 c.c.
Quantity KCl dialysed	19 mgrm.	24 mgrm.	22 mgrm.	14 mgrm.
Per cent. KCl dialysed	38%	48%	44%	28%

TABLE C.—*Collodion Membrane Impregnated with ·2% Cholesterol Tested against Plain Collodion Membrane as Regards Diffusion of Na and K Salts.*

NaCl.			KCl.		
	Cholesterol membrane.	Plain membrane.		Cholesterol membrane.	Plain membrane.
·8% N.S. inside membrane	50 c.c.	50 c.c.	·1% KCl sol. inside membrane	40 c.c.	40 c.c.
Distilled water outside membrane	50 ,,	50 ,,	Distilled water outside membrane	40 ,,	40 ,,
Amount of salts diffused out	·078 grm.	·23 grm.	Amount of salts diffused out	·0029 grm.	·025 grm.
Percentage of salts diffused	19·8%	57·5%	Percentage of salts diffused	6·4%	55·5%

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The following conclusions are of importance: From Table A it will be observed that lecithin seems to have a retentive action on potassium ions within the membrane. The sodium ions dialyse unchanged in comparative concentrations. Table B shows that as more potassium ions pass through the membrane, from without inwards when brain extract is present within, than in the control experiment. Regarding Table C, here it is possible that the cholesterol has lessened the molecular spaces in the membrane, and thus slowed up the diffusion. The percentage diffusion is markedly lessened with both salts, but more so with the potassium.

The quantity of cholesterol per sq. cm. of membrane is extremely small; the membranes used were very thin.

Cataphoresis.

Emulsions of varying quantities of alcoholic solutions of lecithin and cholesterol were made up in a ·1% Na_2CO_3 solution. An amount of each concentration was used in the respective emulsions, so that the total colloid present should remain the same. The voltage used was 120 for 15 minutes in all cases.

Concentrations.			Velocity of particles (cm.).
Lecithin alone			1·0
Cholesterol and lecithin		1 : 1	·5
,,	,,	1 : 2	·5
,,	,,	1 : 3	·6
,,	,,	1 : 4	·8

From this it would seem that cholesterol has a restraining effect on the anionic movement of lecithin.

It was extremely difficult to find a suitable electrolytic medium for suspension of cholesterol alone in colloid form, and not possible to use Na_2CO_3, but it was eventually found that a perfect colloid was obtained by using ·1% glucose solution and forcing into it an alcoholic solution of cholesterol, giving a final concentration of ·1% cholesterol—a similar method to that adopted with Na_2CO_3. In this cholesterol colloid the velocity of the particles was found to be ·3 cm. in 15 minutes. This observation corroborates the above findings.

Lipoid Content of Blood in Certain Conditions.

Process for total cholesterol in blood and tissue.—10 c.c. to 20 c.c. of blood or 5 grm. of tissue is taken. The blood is drawn off and

immediately forced into 50 c.c. of absolute alcohol and allowed to stand for two hours. The tissue, brain or liver, etc., is cut up finely and treated in 30 c.c. absolute alcohol for two hours, then more finely ground in a small mortar. The following steps apply to either blood or tissue: The mass is filtered through a fine filter-paper on a Buchner funnel and washed with hot alcohol, using about 100 c.c. Then about 30 c.c. of ether is slowly poured through and the pump left running until the filterings are dry. The filtrate is set aside. The mass on the filter-paper is then powdered, placed in a fat-extraction thimble in a Soxhlet apparatus and extracted with ether for about four hours. The extract is then added to the original filtrate. The ether is now evaporated off on a water-bath, care being taken to extinguish the flame. About 10 c.c. distilled water is added, together with 2 grm. KOH, and this is stirred into the remaining alcohol. The whole is now evaporated to dryness, during which process saponification of the fats takes place. 75 c.c. distilled water is added, the soaps dissolved and the solution placed in a separating funnel. 75 c.c. of ether is now added, and the separator contents shaken briskly for about one minute.

A few drops of chloroform added to the ether aids the solution of the cholesterol. Separation takes place overnight. The bottom layer is run off into another separator. The ether layer is washed with a little water, and this water added to the above. In the second separator the same procedure is carried out as for the first, with similar quantities of extractive. A third extraction completes this step in the process. The ether extracts are added together and delivered into a weighed flask, the ether evaporated off in hot water, the flask placed in vacuum in a desiccator until thoroughly dry, then weighed.

Test of the process.—20 mgrm. of cholesterol was added to 10 c.c. of defibrinated sheep blood, the cholesterol content of which was previously ascertained. The process was carried through as above.

After deducting the quantity originally present in the blood used 21 mgrm. cholesterol was recovered—a quantity very slightly increased, but well within the range of experimental error.

Process for phospholipin (ether-alcohol soluble phosphorus) in blood and tissues.—The technique in the first steps is similar to that for cholesterol, the only difference being that the ether-alcohol extract is evaporated with 2 grm. phosphorus-free calcium carbonate to dryness. The mass is then ignited until all organic matter is driven off, cooled, and about 50 c.c. of water added. The mixture is

now treated with hydrochloric acid in excess, slightly heated until solution takes place, and filtered. To the filtrate an excess of ammonium hydroxide is added, producing a precipitate of calcium phosphate. This is dissolved in excess of nitric acid and the solution boiled for a short time. Ammonium molybdate solution, specially prepared in the laboratory, is now added, sufficient to precipitate the phosphorus. The yellow precipitate is allowed to settle, filtered, washed well with dilute HNO_3, dried and weighed on a porous glass filter. From this figure, using suitable factors, a very fair estimate of the quantity of phospholipin calculated as lecithin can be obtained.

Blood Cholesterol: Results.

Primary Dementia.

	Percentage of whole blood (grm.).	Age.
A. M—	·030	38
R. M—	·055	32
J. D—	·035	30
A. A—	·067	26
F. W. I—	·030	38
H. L—	·034	25
M. F—	·085	32
W. N—	·075	34
D. H—	·055	25
J. W—	·050	16

The blood phospholipin, calculated as lecithin, varied within very small limits, the average of all cases being ·32% of whole blood. We found the normal figure to be ·30%.

Recurrent Mania.

	Percentage of whole blood (grm.).	
*H. F—	·10	Fairly normal at present.
†A. R—	·32	Just recovering from an attack.
E. R—	·19	Proceeding towards an attack.
A. J. T—	·24	Just recovering from an attack.
J. W. D—	·34	During an attack.
E. H—	·18	Fairly normal at present.
*H. F—	·46	During apex of attack.
†A. R—	·22	Much less excited.

The phospholipin in this condition does not vary very much from normal—not sufficient to merit any comment. The average figure equals ·313% of whole blood.

In primary dementia the average ratio of phospholipin to cholesterol is as 6 : 1. The same ratio figure during the attack of mania is as 1 : 1. Normally this ratio is slightly over 2 : 1.

Cholesterol Content of Brain.

Name.		% of cholesterol (grm.).	Amount in both hemispheres (grm.).	Case.
F. M. H—	(F.)	2·82	30·0	Fairly normal.
A. R—	(F.)	1·87	18·52	C.V.D.
H—	(F.)	1·90	19·0	Epilepsy.
C. H—	(M.)	·52	5·38	G.P.I.
C—	(M.)	·62	6·44	,,

Cholesterol and Phospholipin in Medulla and Pons (mixed).

			grm. %.
C. B—	Fairly normal brain	Cholesterol	4·4
		Lecithin	6·72

Ratio cholesterol to lecithin = 1 : 1·52.

Nitrogen Metabolism.

Processes.—The total nitrogen was estimated by the Kjeldahl method, the urea nitrogen by the hypobromite method. This method gives rather high results, and the error was found experimentally and deducted in each case. The ammonia nitrogen was estimated by Shaffer's vacuum method, the creatinine by the Jaffee reaction, finishing in a Dubosc colorimeter.

The study of the nitrogen metabolism was carried out in twelve cases of primary dementia. The patients under consideration were all given the same diet. Three days were allowed to elapse, then a 24 hours' collection of urine was obtained. The protein in the diet was then increased by 50% and continued for three days, at the end of which period another 24 hours' sample of urine was taken. During these periods any food left was weighed and deducted from the individual's diet. The total volume of urine was taken, and immediately preserved by the addition of a few c.c. of thymol in chloroform preparatory to analysis.

Diet.

Protein	94	grm.	per head per day.
Carbohydrate	342	,,	,, ,,
Fat	57	,,	,, ,,

In the second study 50% more protein was added daily.

Results: Average of Studies; Daily Excretion in Grammes.

	1. Ordinary diet.	2. Increased protein diet.
Total nitrogen . . .	10·91	10·84
Urea ,, . . .	9·92	9·70
Ammonia nitrogen . .	·40	·52
Creatinine	1·44	1·62

It would appear from the fact that the increased protein diet has had no effect on the nitrogen output, that cellular metabolism in dementia præcox is not capable of stimulation in this way. The normal response would be a definite increase of urea nitrogen.

Discussion and Clinical Considerations.

Attention has been previously drawn by one of us (3) to the fact that, by analogy with exactly similar states present after death from malaria definitely associated with lack of oxidation, the arachnoidal opacities and congestive areas in the meninges met with so frequently in *post-mortems* in cases of mental disorder are probably due to deficient oxidation and to the demand of the neuron for oxygen. As regards nervous metabolism, certain outstanding facts strike one at once: firstly, the enormous amount of oxygen consumed by the brain of a waking animal, *viz.*, 360 mgrm. per gramme per minute, as compared with that of skeletal muscle—4 mgrm.—and of salivary glands—28 mgrm.; secondly, the high percentage of phospholipins present, substances intimately bound up with the activation of vital processes; and thirdly, the presence of cholesterol in great excess as compared with other tissues. Cholesterol must obviously be of great importance in nerve metabolism, and from the evidence now put forward, experimental and clinical, it cannot be doubted that its ratio to the phospholipins is a fundamental factor in the pathology of certain forms of mental disorder, and that determination of the blood-cholesterol content is essential to correct diagnosis. It is well, perhaps, here to lay emphasis on the fact that gravimetric estimations should be employed, as the colorimetric methods at present in use have serious defects, leading to erroneous results.

It is a well-known property of phospholipins that they oxidize readily and spontaneously. Matthews (2) states: "The fact that this fundamental stratum of living matter has the power of taking up oxygen, of burning itself and possibly inducing oxidation in

substances dissolved in it, is of the greatest importance for the theory of the mechanism of respiration, since all protoplasm has also the power of reduction or auto-oxidation." Further, "It is very suggestive that the oxidized phospholipin has a much greater affinity for water than the unoxidized. Possibly this process may play a part in cell mechanics, since most movements in cells are apparently due to this changing affinity for water. By oxidation the phospholipin may be made to take up water—by reduction, to lose it." To effect this we have now demonstrated that it must be delicately balanced with an appropriate amount of cholesterol.

The affinity of lecithin for water is clearly evidenced in Table A.

Quite recently it has been shown by workers in Japan (9) that calcium and cholesterol injected into rabbits cause histological changes in nerve-cells, indicating a dehydration or shrinkage of the cell, while lecithin and potassium, contrariwise, cause a swelling or hydration.

The amount of cholesterol present in normal blood is ·15 grm.% and of lecithin ·30, and such a ratio would seem to be necessary for the adequate control of oxidation processes. Decrease the cholesterol and the lecithin is at once attacked, as there is little variation in the percentage of lecithin. The seriousness of any alteration, especially diminution, in the cholesterol content is apparent.

It is presumable that just as phosphate activates oxidative processes in ordinary fermentation, so the phospholipins accelerate the energizing of protein, sugar and fats, and that such action is regulated by the amount of cholesterol in association with them.

The union of cholesterol and lecithin would appear to be one of adsorption, as shown by the cataphoresis experiments. The charge on the cholesterol particles is slightly anionic, and intermediate in degree between the markedly anionic charge on lecithin and that of albumens and globulins, which is cationic. In the medium in which it exists in the body fluids it is possible that it may act in an amboceptor-like fashion.

Owing to the excessive demands of nervous tissue in respect of oxygen, any lack on the part of the blood will at once result in disordered functioning of the neuron. How will it respond? By increased action of its endocellular ferments and stimulation of the energizing mechanism of the systemic organization—gonads, thyroid, adrenals, circulatory apparatus, etc. If this state of anoxæmia persists the result must be neuronic exhaustion, hyperactivity of the sympathetic system and various ductless glands, general imbalance, serious disorder of cellular metabolism, and

eventually neuronic deterioration and destruction. Consequent on this there will be a state of cellular acidosis.

Hypercholesterinæmia, which we have shown to exist in certain states of mania, will, owing to abnormal inhibition by the excess of cholesterol, result in an anoxæmia of the tissue-cells, but it is obvious that anoxæmia produced in this manner will have a less destructive effect on the neuron, since ferment action will also be inhibited. The hypercholesterinæmia associated with the climacteric period (4) is of much interest in connection with the nervous pathology of this time of life, and since quite recently a hypercholesterol content of tissues has been noted (5) as a factor contributing to the preparation of a precancerous ground, this may have some bearing on the lower mortality from cancer in the population of mental hospitals, since such a large proportion are subjects of dementia præcox. The remarkable deficiency of cholesterol in the brain of general paralytics is worthy of note, and it is an interesting speculation whether some deficiency of this nature may not in certain cases of syphilis have a bearing on the initiation of infection of the central nervous system.

As regards treatment, the indication is, of course, restoration of the normal blood cholesterol as quickly as possible, and recovery will obviously depend very largely on recognizing the condition at an early stage before the neuron is irretrievably damaged.

With regard to pyretotherapy, increased body temperature will, of course, tend to mobilize cholesterol, and temporarily result in its increase in colloid form in the body fluids.

Other points of interest in relation to the cholesterol blood content are the facts that there is evidence of its increase after castration and splenectomy (6), and that a distinct diminution is caused in dogs by thyroid feeding (7), best marked when the symptoms of thyroid excess are most pronounced.

In view of the frequency with which profound degenerative changes are noted in the adrenal cortex at *post-mortems* in cases associated with certain forms of mental disorder and infection, the relation between the cholesterol blood content and adrenal cortex is of special interest; evidence has recently been brought forward(8) that extracts of adrenal cortex cause, in a normal animal, a lowering of blood cholesterol, and on prolonged administration a rise in the total cholesterol of the body. In this the reticulo-endothelial system is concerned, as when this system is blocked no reduction occurs in blood cholesterol after cortical injections. After such injections to mice cholesterol accumulates in the body

generally. This, along with the lowering of blood cholesterol, points to a cholesterol-fixing action of the cortical active principle.

In cases of dementia præcox we are endeavouring to increase the cholesterol blood content directly by parenteral injections of this substance dissolved in olive oil, and also by feeding with cholesterol emulsions and colloids.

The following case is worthy of mention, as such rapid and complete recovery is rarely met with: H. L—, a very definite early case of dementia præcox, æt. 25, admitted from general hospital, where she was sent for observation. Duration of illness four weeks. School history good; had reached highest standard. On admission blood cholesterol content ·03 grm.%. Parenteral injections of ·25 grm. cholesterol in olive oil were given every third day, and suitable diet calculated to aid cholesterol production. After a month she was given, by mouth, ·5 grm. of cholesterol daily in emulsion, which was continued for a further two months. Steady and continuous mental improvement took place during the treatment, with synchronous increase of blood cholesterol. At the end of three months her blood-cholesterol content was normal and she appeared quite recovered. She was kept under observation for a further period of two months without treatment. No relapse occurred and she was discharged recovered, and has remained quite well since.

Summary.

The following facts are demonstrated:

(1) The inhibitory influence of cholesterol on hæmolysis and its activation by lecithin, also the presence of a thermolabile ferment in serum which activates hæmolysis, and which appears to vary directly with the blood cholesterol content.

(2) The influence of cholesterol as a controlling factor in oxidative processes, its controlling power being best exercised in relation to lecithin in the ratio to that substance normally existing in blood.

(3) That lecithin has an attractive influence on potassium ions, and that the presence of cholesterol in the membrane definitely retards diffusion of potassium.

(4) The retarding effect of cholesterol on the anionic movement of colloidal lecithin.

(5) That increase of protein diet has no effect in stimulating metabolism in dementia præcox.

(6) That the blood-cholesterol content in dementia præcox is

greatly diminished, while abnormal increase is noted in states of mania.

(7) That in general paralysis there is great diminution of cholesterol in the brain substance.

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