THE CLINICAL STUDY OF HYPERCHOLESTERINEMIA *

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That lipoidal substances play an important rôle in the animal body is now generally recognized. They occur in practically all the body-tissues and the amounts are increased in sclerotic blood-vessels,¹ in the white plaques of retinitis,² in xanthomata, in old infarcts, in caseous tuberculous material and in the cholesteatomatous tumors of the ear and cranial cavity. The activity of certain anesthetics varies with their lipoidal solubility and hemolytic processes may be accelerated or retarded by the presence of lipoids. Quite recently a number of relatively simple methods have been described for determining the amounts of lipoids, and especially of cholesterin, in small quantities of blood or blood-serum. As a result, data concerning the quantity of cholesterin in normal and pathological bloods are now rapidly accumulating. It is the purpose of the present paper to review these recent studies of cholesterinemia and to present a series of personal observations.

The methods used for determining the amount of cholesterin in the blood depend on a variety of principles. Since free cholesterin protects red corpuscles from hemolysis by saponin, it has been proposed to estimate the amount of free cholesterin in the blood-serum by determining the degree to which the serum will protect washed red cells from hemolysis by saponin.³ In most other methods the cholesterin is first extracted from the blood or serum and the amounts extracted are then determined either by direct weighing, by weighing after precipitation with digitonin, or by colorimetric methods. The extraction is of great importance because cholesterin is present in the blood largely in combination with fatty acids or other substances and the amount extracted depends on the degree to which these combinations are broken up. For this reason the simple extraction of dried blood or blood-serum in the Soxhlet apparatus

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1. Windaus: Ueber den Gehalt normalen und atheromatösen Aorten an Cholesterin und Cholesterinester, *Ztschr. f. physiol. Chem.*, 1910, lxxvii, 174.

2. Chauffard, A., de Font-Réaulx and Laroche, G.: Nature cholestérinique des plaques blanches rétiniennees dans un cas de rétinite albuminurique, *Compt. rend. Soc. de Biol.*, 1912, lxxiii, 283.

3. Boidin, L., and Flandin, C.: Procédé rapide de diagnostic de l'hypercholestérinémie à l'aide de la saponine, *Compt. rend. Soc. de Biol.*, 1912, lxxii, 28.

uniformly fails to yield the total free and combined cholesterin present. The method which we have used is based on the methods described by Grigaut⁴ and by Weston and Kent.⁵ In extracting we followed the method of Grigaut, in which a preliminary treatment of the blood-serum with an alkaline alcoholic solution at a high temperature is used to break up the cholesterin compounds. The colorimetric estimation of the amounts of cholesterin subsequently extracted was made according to the modification of Salkowski's test described by Weston and Kent.

TECHNIC

In brief, our procedures were as follows:

Two c.c. of blood-serum were placed in a pressure bottle of 150 c.c. capacity. To this was added 20 c.c. of 1 per cent. solution of potassium hydroxid dissolved in 50 per cent. alcohol. The cover was screwed down and the whole placed in a boiling water-bath for from fifteen to twenty-minutes. After removal from the water-bath, the contents of the pressure bottle were allowed to cool and were then shaken with 50 c.c. of ether. The ether was decanted into a separating funnel and 30 c.c. more of ether was added to the remaining fluid and shaken vigorously as before. This was again decanted into the funnel and any aqueous liquid which separated from the ether was removed. This was then washed with 80 c.c. of distilled water. The ethereal extract, after separation from the wash water, was poured into an evaporating dish and evaporated nearly to dryness, leaving behind the small yellow oily droplets containing the cholesterin. Five c.c. of chloroform (Merck's blue label) was then placed on the evaporating dish and rotated carefully so as to dissolve the oily droplets as completely as possible. This chloroform solution was transferred to a convenient receptacle, and a second 5 c.c. of chloroform was then used to wash the evaporating dish and were added to the first 5 c.c.

The amount of cholesterin in the chloroform solution was determined by comparing its color reaction with those of cholesterin chloroform solutions of known strength. These standard solutions were prepared by dissolving Merck's cholesterin in pure chloroform (Merck's blue label) and by preparing a series of dilutions of varying strength so that the amount of cholesterin in 1 c.c. of chloroform varied from 0.0002 to 0.0004 gm. A set of test-tubes of uniform bore were arranged in a rack and 1 c.c. each of the known solutions of cholesterin were added in ascending series, as was also 1 c.c. of the cholesterin solution prepared from the blood-serum. It was often necessary to dilute the latter so that the amount would fall within the scale of the known quantities. To each tube was now added 0.1 c.c. of concentrated sulphuric acid, and the mixture was thoroughly shaken. After thirty minutes 1 c.c. of chloroform was added to each tube and after being placed for fifteen minutes in a dark room, the color of the unknown solution was compared with that of the known. This method was found to be exceedingly sensitive and differences in the original fluid of 0.00005 gm. per c.c. could be detected. Successive readings from the same serum also gave concordant results, and even after several days' standing, little or no diminution in the amount of the cholesterin in the serum could be discovered.

4. Grigaut, A.: Sur le dosage de la cholestérine dans les tissus, *Compt. rend. Soc. de Biol.*, 1911, lxxi, 441.

5. Weston, P., and Kent, G.: Determination of the Cholesterol Content of Human Serum by the Colorimetric Method, *Jour. Med. Research*, 1912, xxvi, 531.

THE AMOUNT OF CHOLESTERIN IN NORMAL BLOOD

The amounts of cholesterin in normal blood-serum found by various observers who have used methods similar to the preceding, have been fairly concordant. Thus Grigaut placed the normal limit from about 1.2 to 1.8 gm. per liter of blood-serum, Weston and Kent⁵ found from 1.17 to 2.97 with an average of 1.82 gm., Henes⁶ found from 1.4 to 1.8 gm. per liter of blood-serum, and Widal, Weill and Laudat⁷ found 1.74 and 1.95 in two normal fasting individuals. Iscovesco⁸ has described a more elaborate extraction method, which apparently yields somewhat larger quantities than the above.⁹ As will be seen from Table 1, the cholesterin in normal blood-serum as estimated by the method which we used, varied between 1.20 and 1.75 gm. per liter. Amounts of 2.0 gm. per liter or over may be regarded as definitely pathological. When those with marked thickening of the peripheral arteries and high blood-pressure were excluded from consideration, the age of the individual did not influence the amount of cholesterin in the serum. This is of interest in view of the fact that Wacker¹⁰ observed an increase in the cholesterin content of the reserve fat of aged persons, and Robertson and Burnett¹¹ have advanced the view that an accumulation of cholesterin in the body may account for the well-known incidence of carcinoma with advancing age.

TABLE 1.—CHOLESTERIN IN NORMAL BLOOD-SERA

Age	Observations	Amount in Gm. per Liter
10-19	1	1.40
20-29	5	1.60-1.27-1.75-1.45-1.50
30-39	3	1.65-1.25-1.35
40-49	1	1.20
50-59	3	1.45-1.55-1.20
60-69	4	1.30-1.20-1.30-1.35

The cholesterin of the blood is not distributed evenly between the plasma or serum on the one hand and the red corpuscles on the other. Iscovesco¹² found varying relations between the two. Henes⁶ found that on the average 54.5 per cent. of the blood cholesterin was present in the

6. Henes, E.: Untersuchungen über den Cholesteringehalt des menschlichen Blutes bei inneren Erkrankungen, *Deutsch. Arch. klin. Med.*, 1913, cxi, 122.

7. Widal, Weill and Laudat: La lipémie des brightiques, *Semaine méd.*, 1912, xxxii, 529.

8. Iscovesco, H.: *Compt. rend. Soc. de Biol.*, 1912, lxxii, 257.

9. Defaye: La cholestéremie, *Etudes cliniques*, Univ. de Bordeaux, No. 126, 1911-1912. Quoted by Henes.

10. Wacker, L.: *Ztschr. f. physiol. Chem.*, 1912, lxxx, 383.

11. Robertson and Burnett: Preliminary Communication on the Part Played by Cholesterol in Determining the Incidence of Carcinoma, *Proc. Soc. Exper. Biol. and Med.*, 1913, x, 140.

12. Iscovesco, H.: Les lipoides du san: Dosage comparatifs des lipoides des globules frais et de sérum, *Compt. rend. Soc. de Biol.*, 1912, lxxii, 985.

serum and 45.5 per cent. was in the corpuscles, so that when the serum was used for determinations the results were higher than when the whole blood was used. Grigaut and L'Huillier¹³ obtained similar results in normal individuals, but they found that in pathological conditions the amounts in red blood-corpuscles remained fairly constant, even when the amounts in the blood-serum varied widely. For this reason the blood-serum is, as a rule, a more sensitive indicator of pathological changes than is the whole blood, and we have, therefore, made all of our determinations with blood-serum.

A number of authors have studied the effect of cholesterin ingestion on the cholesterin content of the blood. While some have failed to observe any relation between diet and cholesterinemia or between the amount of cholesterin taken by mouth and the amount in the blood, a number of recent workers have confirmed the opinion of those who have held that the cholesterin of the body is derived, in part at least, from the cholesterin in the food.¹⁴ Thus Grigaut and L'Huillier¹⁵ were able to raise the cholesterin content of a dog's blood from 1.8 to 3.0 gm. per liter by feeding 1 gm. of cholesterin a day, and in another animal the content was raised from 1.8 to 3.8 by feeding 2 gm. of cholesterin a day. After the feeding was discontinued the amounts of cholesterin in the blood-serum returned to normal rather rapidly. Similar observations with similar results have been made on man by Widal, Weill and Laudat, by Henes and by Lemoine and Gérard.¹⁶ The cholesterin content of the blood may be raised either by feeding pure cholesterin or by giving a diet rich in this substance.

PATHOLOGICAL VARIATIONS IN THE CHOLESTERIN CONTENT OF THE BLOOD

It has long been known that the serum of certain patients is milky instead of being clear. These lactescent serums are in general associated with increases in the amounts of lipoid substances in the blood as determined by chemical methods, and in general also with hypercholesterinemia. Widal, Weill and Laudat⁷ have shown, however, that the lipoids may be increased even though the serum is not milky and that no close parallelism exists between the degree of lactescence and the amounts of lipoids determined chemically.

13. Grigaut and L'Huillier: Taux comparé de la cholestérine des hématies et du sérum dans le sang normal et pathologique, *Compt. rend. Soc. de Biol.*, 1912, lxxiii, 202.

14. Doree, Gardner, Fraser, Ellis: Origin and Destiny of Cholesterol in the Animal Organism; a series of papers in the *Proc. Royal Soc.*, 1908 to 1912.

15. Grigaut and L'Huillier: Hypercholesterinémie d'origine alimentaire chez le chien, *Compt. rend. Soc. de Biol.*, 1912, lxxiii, 304.

16. Lemoine, G., and Gérard: Variations du taux de la cholestérine par rapport à l'alimentation, *Bull. et mém. Soc. méd. d. hôp.*, 1912, 931.

Hypercholesterinemia has been frequently encountered in diabetes. Grigaut and Chauffard mention such an increase frequently. Bürger and Beumer¹⁷ found an increase in four out of five diabetics, three of whom had milky serums. Henes found an increase in two out of seven patients. Apert, Pechry and Rouillard¹⁸ were unable to find any definite increase in most of the diabetics whom they examined.

Our own observations on patients with diabetes are shown in Table 2. It will be seen that pathological increases of the cholesterin were present in six of ten patients, and that the largest amount occurred in a patient with diabetic coma. In two of the patients the cholesterinemia was increased after the sugar had been removed from the urine by placing the patients on a standard Von Noorden carbohydrate-free diet. Whether this rise was due to an increased amount of cholesterin in the diet or to an increased mobilization of lipoids already in the body, I am unable to say.

TABLE 2.—CHOLESTERINEMIA IN DIABETES

Name	Age	Blood-pressure	Sugar in urine	Cholesterin in gm. per liter	Remarks
Str.	20	120	7.0%	3.2	Severe case.
Bri.	56	145	4.5%	4.15	Coma. Mastoiditis.
LaF.	39	130	{ + 0	{ 2.8 3.3	Diabetic gangrene.
Wil.	63	175	{ + +	{ 2.25 1.7	
McB.	53	135	{ + 0	{ 1.7 1.9	Mild case.
Wic.	38	130	{ 6.8% ++	{ 2.8 3.	
Fee.	8	110	++	3.	Severe case.
Dib.	58	135	+	1.3	Very mild case.
Bar.	40	140	+	1.75	Very mild case.
Hil.	30	?	+	1.8	Mild case.

In jaundice due to an obstruction of the common bile duct there is uniformly present a hypercholesterinemia. Chauffard, LaRoche and Grigaut¹⁹ have ligated the common bile duct in the dog and have found that the amounts of cholesterin in the serum rose from the normal of 1.75 gm. to amounts which varied between 2.4 and 5.4 gm. per liter. These same authors²⁰ have shown that hypercholesterinemia may also result from a clinical obstruction of the common bile duct, whereas in hemolytic jaundice the amount of cholesterin in the blood-serum is not increased. In five patients with obstructive jaundice whom we have

17. Bürger, M., and Beumer: *Zur Lipoidchemie des Blutes*, Berl. klin. Wehnschr., 1913, xx, 112.

18. Apert, Péchery, and Rouillard: *Mesure de la cholestérinémie chez les diabétiques*, Compt. rend. Soc. de Biol., 1912, lxxii, 822.

19. Chauffard, Laroche and Grigaut: *Recherches expérimentales sur la cholestérinémie après ligature du cholédoque*, Compt. rend. Soc. de Biol., 1913, lxxiv, 1093.

20. Chauffard, Laroche and Grigaut: *Le taux de la cholestérinémie chez les hépatiques*, Compt. rend. Soc. de Biol., lxx, 1911, 20.

studied there were definite increases in the amount of cholesterin in the blood. It seems evident, therefore, that common duct obstruction will lead to an increased amount of cholesterin in the circulation. Whether this is dependent entirely on a resorption of the bile or whether it is due in part to an associated disease of the liver, does not seem to be established at the present time.

TABLE 3.—CHOLESTERINEMIA IN JAUNDICE

Name	Cholesterin in gm. per liter	Diagnosis
Wo.	3.50	Infectious (or catarrhal) jaundice.
Gr.	2.95	Common duct stone with jaundice.
Ch.	2.85	Common duct stone with jaundice.
Sh.	3.80	Malignant obstruction of the common duct.
Tri.	3.90	Malignant obstruction of the common duct.

Hypercholesterinemia occurs with frequency in patients with chronic Bright's disease, high blood-pressure and related conditions.^{21, 7} I have devoted considerable attention to this group of cases with the hope that some relation might become evident between the hypercholesterinemia and the individual manifestations of cardiorenal disease. Our results which are shown in Table 4 have been arranged in the following order: the first four patients showed marked thickening of the peripheral arteries, but had no increase in blood-pressure and no albumin in the urine. The cholesterinemias in these patients were 2.25, 2.3, 1.80 and 1.95, respectively. The next group of patients showed chronic arterial hypertension without albumin in the urine. In this group the cholesterinemias were 2.0, 2.37, 1.95, 2.75, 1.85, 1.25, 3.2 and 3.3 gm. per liter. The third group includes those with chronic hypertension and albumin in the urine, but with good functional tests of the kidneys. In this group of patients, the figures were 2.0, 5.3, 3.85, 3.85, 1.25, 2.15, 1.75, 2.1, 2.25, 2.97. The final group includes those who showed more or less renal insufficiency as judged by the phenolsulphonephthalein test and an increase of hypobromite "urea" in the blood. They are arranged according to the degree of renal insufficiency, the more severe ones being placed last. The cholesterinemias in this group of patients were 3.5, 4.0, 1.35, 1.95, 1.85, 1.6, 1.73, 0.85, 0.8. In the first three of the preceding groups a hypercholesterinemia of moderate grade was encountered in the majority of the patients. Some of the lower figures may possibly have been due to an associated edema. It is interesting that we should have found an increase in the amount of cholesterin in two of four patients selected on account of a marked thickening of the peripheral arteries who

21. Chauffard, Laroche and Grigaut: Le taux de la cholestérinémie au cours des cardiopathies chroniques et des néphrites chroniques, *Compt. rend. Soc. de Biol.*, lxx, 1911, 108.

TABLE 4.—CHOLESTERINEMIA IN VASCULAR AND RENAL DISEASE

GROUP I							
Name	Age	Blood-pressure	Urine	Peripheral Arteriosclerosis	Cholesterin in gm. per liter	Phthalein output	Hypobromite "Urea"
En.	59	145	neg.	marked	2.25		
Her.	49	154	neg.	marked	2.30	71.2	.25
Rey.	67	120	neg.	marked	1.95		
Wal.	75	120	neg.	marked	1.80		
GROUP II							
Mus.	..	170	neg.	marked	2.00	75.0	.22
Mil.	68	180	neg.	marked	2.37		
Dun.	53	180					
		210	neg.	marked	1.95	63.3	.31
Bri.	73	190	neg.	marked	2.75		
McD.	77	240	neg.	marked	1.85		
Lai.	56	210	neg.	marked	1.25	48.8	.59
						28.0	
Rus.	59	210	neg.	?	3.2	60.5	.65
Fos.	49	180	neg.	neg.	3.33	35.9	.44
						59.	
GROUP III							
Cam.	38	210					
		130	Hy.	mod.	2.0	72.	.36
Hat.	43	230	casts				
		230	Alb. and casts	slight	5.3	40.	.48
Ske.	39	210	Alb. and casts	slight	3.85		.51
Rey.	46	212	Alb. and casts	marked	3.85	77.5	.31
Hep.	47	230	Alb. and casts	marked	1.25	60.0	.46
Dew.	65	205	Alb. and casts	marked	2.15		.5
Van.	58	170	Alb. and casts	marked	1.75	42.2	.38
Owe.	52	...	Alb. and casts	marked	2.10	74.7	.65
Ant.	45	235	Alb. and casts	Mod.	2.25		
Mil.	44	265	Alb. and casts		1.97		
GROUP IV							
Doa.	48	172	Alb. and casts	Neg.	3.5	26.2	.34
May.	26	250					
		230	Alb. and casts	Neg.	4.0	34.0	.71
Wald.	54	190	Alb. and casts	Mod.	1.35	23.9	.53
Mor.	47	204	Alb. and casts	marked	1.95	22.3	.80
Mur.	58	225	Alb. and casts	marked	1.85	12.	1.55
Jac.	48	170	Alb. and casts	Mod.	1.45		
					1.6		
					2.1		
Jacks.	45	245	Alb. and casts	marked	1.73	6.8	2.02
Gar.	40	105	Alb. and casts	Mod.	.85	.0	4.39
Eclampsia..	..	...	Alb. and casts		.08		

showed no evident signs of kidney disease; for Chauffard²² and Henes⁶ found no definite relation between arteriosclerosis and cholesterinemia. In patients with high blood-pressure but without albumin in the urine and without other signs of nephritis, hypercholesterinemia is also common. Of the first three groups, the hypercholesterinemia is most marked in the third in which the high blood-pressure was associated

22. Chauffard, A.: Les dépôts locaux de cholestérine et leur rapports avec cholestérinémie, *Rev. de med.*, 1911, xxxi, 176.

with evident renal disease. The study of Group IV shows that when there is marked renal insufficiency, as measured by the phthalein test and by the accumulation of hypobromite "urea" in the blood, the cholesterin content of the serum tends to fall and may even become subnormal. Similar observations have been made by others,²¹ and Widal, Weill and Laudat⁷ stated that they were able to follow three patients in whom a fall of the cholesterin in the blood coincided with a rise of the incoagulable nitrogen. It seems evident from these observations that a hypercholesterinemia cannot be regarded as an index of renal insufficiency, for it may be present in cases without manifest renal disease, and it usually falls at the time of maximum retention of the urinary products. So far as our observations go, it would seem that a hypercholesterinemia may be associated with the degenerative processes in the blood-vessels without manifest renal disease.

Chauffard and his school have studied the amounts of cholesterin in the blood during acute and chronic infections, and they have found that whereas in febrile tuberculosis the amount of blood cholesterin is diminished,²³ in typhoid fever it tends to be increased during the later stage of the disease.²⁴ They have also shown that in the later stages of pregnancy there is an increased cholesterinemia.²⁵ I have made no special study of these conditions, but have determined the cholesterin content of the blood in various conditions selected at random. Of these I wish to mention especially the case of a young girl with multiple tumors in the subcutaneous tissues which clinically resembled neurofibromas who had 5.63 gm. of cholesterin per liter of blood-serum. Unfortunately, it was not possible to remove one of the tumors for microscopic examination.

THE RELATION OF CHOLESTERINEMIA TO LOCAL CHOLESTERIN DEPOSITS

It has been mentioned that in certain pathological conditions there are abnormal deposits of cholesterin in the body, and the question arises as to the relation which may exist between such deposits and an increased cholesterin content of the blood. It is conceivable, for example, that the local deposits may depend entirely on local conditions which either favor a deposit of cholesterin from normal body fluids or which may possibly lead to a local production of cholesterin. The cholesterin deposits in infarcted areas and in tuberculous caseous material seem to be due to such local changes; and it has been shown²³ that in tuberculosis the cholesterin of the blood is normal or diminished. On the other

23. Chauffard, Richet and Grigaut: La cholestérinémie au cours de la tuberculose pulmonaire, *Compt. rend. Soc. de Biol.*, 1911, lxx, 276.

24. Chauffard, Laroche and Grigaut: Évolution de la cholestérinémie chez les typhiques, *Compt. rend. Soc. de Biol.*, 1911, lxx, 70.

25. Chauffard, Laroche and Grigaut: Evolution de la cholestérinémie au cours de l'état gravidique et puerpéral, *Compt. rend. Soc. de Biol.*, 1911, lxx, 536.

hand, the cholesterin deposits may be regularly associated with such marked degrees of hypercholesterinemia as to favor the view that they result in large part from a surcharging of the blood with this substance. In such cases they may well be compared with the tophi of gout and one may speak of a cholesterin diathesis. Multiple tuberos xanthomas have been shown to be associated with marked local deposits of cholesterin,²⁶ and they are known to occur especially in association with general conditions, such as diabetes and jaundice, in which marked degrees of hypercholesterinemia are apt to be present. Furthermore, they have been shown to be associated with high degrees of cholesterinemia,^{27, 28} so that they seem to depend on a surcharging of the blood with this substance. According to Chauffard and Laroche,²⁹ a similar relation exists for the more common xanthelasmas of the eyelids which are frequently encountered in chronic jaundice, and in two of four cases these authors demonstrated that xanthelasmas were associated with hypercholesterinemia. Greater interest attaches itself to the relation which exists between hypercholesterinemia and the cholesterin deposits in the blood-vessels, the retinae and the arcus senilis corneae which are so often associated with diseases of the kidneys and of the arteries. We know that hypercholesterinemia is frequent in such patients, and one is tempted to attribute these degenerations in part at least to the hypercholesterinemia present,³⁰ and especially so as Anitschkou³¹ has shown that experimentally one may produce similar changes in the arteries by the administration of cholesterin. On the other hand, the cholesterinemia is by no means constant in these patients, and when present it is usually of moderate degree. Should one assume, therefore, that the cholesterin deposits were secondary to changes in the blood, one must postulate that there had been times of greater cholesterinemia during which the deposits occurred. The proof of such an assumption is not easily furnished and at present it seems more plausible to assume that these cholesterin deposits occurred secondary to degenerative changes in the tissues. Nevertheless the frequent occurrence of hypercholesterinemia in such patients and the experimental work of Anitschkou has opened up the whole subject of the relation of arteriosclerosis to hypercholesterinemia and a solution of

26. Pollitzer, S., and Wile, U. J.: Xanthoma tuberosum multiplex, *Jour. Cut. Dis.*, May, 1912.

27. Thibierge and Wiessenbach: Xanthome tubéreux disséminé et généralisé avec hypercholestérolémie, *Bull. et mem. Soc. méd. d. hôp.*, 1911, xxxi, 93.

28. Legendre, Joltrain and Levy-Franckel: Xanthome disséminé et généralisé avec chéloïdes secondaires, *Bull. et mem. Soc. méd. d. hôp.*, 1912, xxxiv, 539.

29. Chauffard and Laroche: Pathogénie du xanthélasma, *Semaine méd.*, 1910, xxx, 241.

30. Lemoine, G.: Théorie de l'artério-sclérose basée sur la cholestérolémie, *Bull. et mém. Soc. méd. d. hôp.*, 1912, xxxiii, 227.

31. Anitschkou: Die pathologischen Veränderungen innerer Organe bei experimentellen Cholesterinesterverfettung, *Deutsch. med. Wehnschr.*, 1913, xxxix, 751.

this question is all the more urgent for the reason that should there be any relation between hypercholesterinemia and arteriosclerosis it would lead to an endeavor to control the cholesterin content of the blood as a prophylactic measure in the prevention of arterial degeneration.

CONCLUSIONS

By the method which we have used, the cholesterin in the blood of normal individuals is found to vary within rather narrow limits. It was definitely increased in obstructive jaundice, in six of ten patients with diabetes, and most patients with marked thickening of the peripheral arteries, chronic arterial hypertension and chronic nephritis. When, however, there is a marked functional insufficiency of the kidney, the cholesterinemia may fall to normal or even below normal. In a patient with multiple subcutaneous tumors (neurofibromas?) there was a marked hypercholesterinemia. Excepting in the case of obstructive jaundice, where the cause of the hypercholesterinemia is in part at least due to a resorption of bile, little is known about the etiology of pathological increases in the amount of cholesterin in the blood.