THE SIGNIFICANCE OF CHOLESTEROL IN PHYSIOLOGY AND PATHOLOGY:

A CONSIDERATION OF SELECTED PROBLEMS.*

BY

E. NOBLE CHAMBERLAIN, M.D., M.Sc., M.R.C.P.,
HONORARY ASSISTANT PHYSICIAN, ROYAL SOUTHERN HOSPITAL, LIVERPOOL;
LECTURER ON PHYSIOLOGY AND DEMONSTRATOR IN MEDICINE,
UNIVERSITY OF LIVERPOOL.

In this abstract it will not be possible to deal with the physiological aspects of this subject, but certain points must be mentioned briefly in view of their direct bearing on the pathological problems to be considered later.

Cholesterol is excreted from the body through the media of the bile, intestinal mucosa, and skin. The last of these appears to have been neglected in the literature, but since cholesterol is contained in appreciable amounts in the superficial layers of the skin, the desquamation of this will lead to its loss. The lost cholesterol is replenished mainly from food, but at certain times it is probable that a supplementary supply is derived from synthesis. The most likely site for such synthesis is the suprarenal glands. This view was put forward by the French school some years ago, and, though denied by the German school, has received fresh support from personal observations by myself.¹

In spite of the somewhat coarse mechanism of intake and output of cholesterol, the blood cholesterol in an individual remains remarkably constant, suggesting that some finer mechanism is at work. I have shown that the spleen possesses the property of removing excessive amounts of cholesterol from the blood; this, in conjunction with the observations of other writers, suggests the possibility that the spleen may have a function as a regulator of blood cholesterol.

The relations of cholesterol to certain important pathological problems may now be considered, but it must be mentioned that in this abstract it has not been possible to give a complete account of the relationship of cholesterol to pathology, and greater attention has been paid to those problems in which the cholesterol changes are beyond doubt, than to those where such changes are still disputed. The object has been to select certain of the more important pathological problems and discuss their relations with cholesterol, and particularly to endeavour in each case to explain the pathological findings from a physiological standpoint.

Before describing these conditions, it must be mentioned that whenever reference is made to "blood cholesterol" the figures refer to estimations made either on the whole blood or on the plasma, unless it is otherwise stated. The amount in each is approximately the same, but in disease variations are most commonly found in the plasma, and most observations have been made on this part of the blood. Estimations on whole blood, however, also give fairly reliable information, as the amount of cholesterol in the corpuscles remains practically constant. Again, unless specially mentioned, the figures refer to total cholesterol—that is to say, to both free and ester cholesterol.

CHOLESTEROL IN NEPHRITIS.

The first disease to be described here, in which notable changes in cholesterol metabolism have been found, is nephritis. The earlier investigations by Klinkert,² Grigaut, Laroche, Chauffard,³ and Epstein,⁴ showed that blood cholesterol was frequently raised in this condition, but their observations were comparatively few, and little attempt was made to determine whether or not this rise occurred in all forms of nephritis. A recent paper by Maxwell,⁵ however, deals with a large number of cases investigated from this point of view, and many valuable observations have been recorded, some of which have been confirmed by my personal investigations.

The most marked changes in cholesterol metabolism are found in the so-called chronic parenchymatous variety of nephritis, a disease characterized by oedema, marked

albuminuria, and anaemia. Cardio-vascular changes are often present, but do not form a prominent feature of the clinical picture. In this type of disease the blood cholesterol is frequently raised from a normal of 140 to 180 mg. per cent. to figures between 400 and 600 mg. per cent. or more. Usually the rise of cholesterol is more or less proportionate to the degree of oedema present, so that it has been suggested by some authorities that hypercholesterinaemia and oedema are related as cause and effect. As Maxwell points out, however, there are numerous cases in which the degree of oedema and the blood cholesterol do not run parallel, and, in fact, cases are found with a high blood cholesterol and no oedema, so that it is more likely that there is some common cause responsible both for the oedema and the hypercholesterinaemia. With improvement in the clinical condition there is as a rule a fall in the blood cholesterol, often running parallel with the disappearance of the oedema. In certain cases, however, the blood cholesterol remains high after all oedema has gone, and these cases usually have an unfavourable outlook, and the degree of hypercholesterinaemia, therefore, is a sign of some prognostic importance.

In acute nephritis, generally recognized by some degree of oedema, of haematuria and albuminuria, and by its comparatively sudden onset, a similar state of affairs prevails as in chronic parenchymatous nephritis. The blood cholesterol is considerably raised, perhaps to 200 or 300 mg. per cent., but rarely reaches the very high figures sometimes seen in the chronic parenchymatous variety. Its level is also roughly proportionate to the degree of oedema. In cases which subside completely, as do a considerable number of cases of acute nephritis, particularly in children, the blood cholesterol decreases with the clinical improvement, but Maxwell finds that in those cases which progress to chronic parenchymatous nephritis the cholesterol remains high. Here again, therefore, the blood cholesterol may form some index of the progress and ultimate end of the disease.

The type of disease which is commonly called interstitial nephritis is a somewhat ill-defined condition, closely associated with arterio-sclerosis and high blood pressure, and difficult to separate from these conditions. Thus it is not surprising that authorities do not agree on the cholesterol findings. If we accept as a definition of chronic interstitial nephritis a disease characterized by the presence of polyuria, especially nocturnal, by slight albuminuria and nitrogen retention in the blood, estimations of blood cholesterol in such a disease usually reveal no significant changes. If, however, the dominant feature of the disease is arterio-sclerosis, the cholesterol is usually increased to some extent, the figures reaching 200 to 260 mg. per cent.

It is interesting to note here that whilst acute nephritis and the chronic parenchymatous form are associated with considerable oedema and a marked rise of blood cholesterol, the chronic interstitial form, with its small rise of blood cholesterol, is rarely accompanied by much oedema, unless in the terminal phases of the disease as an expression of cardiac failure. This suggests that the two types of the disease are essentially different in their nature, as indeed their causation and general course would lead one to expect.

Epstein⁶ regards chronic parenchymatous nephritis as a metabolic disorder associated in most cases with hypothyroidism. He points out that in both these conditions there is a lowered basal metabolic rate, accompanied by changes in the subcutaneous tissues. Supporting this argument he observes that in hypothyroidism, as in parenchymatous nephritis, there is a rise of blood cholesterol, which, he says, is inversely proportionate to the metabolic rate.

Gardner and Gainsborough,⁷ in some recent investigations on this problem, although they confirmed the work of previous authors, that the blood cholesterol is raised in hypothyroidism and diminished in hyperthyroidism, failed to find any definite relationship between the blood cholesterol and the basal metabolic rate, although in hypothyroidism there was a rough parallelism between the two. Moreover, they drew attention, with justice, to the fact that much higher figures are found for the blood cholesterol in nephritis than ever occur in hypothyroidism. Whilst,

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therefore, we may agree with Epstein and Lande that chronic parenchymatous nephritis is a metabolic disorder, we cannot take the variations in blood cholesterol as indicating any particular relationship between this condition and hypothyroidism.

The interpretation of the marked increase in blood cholesterol in parenchymatous nephritis is therefore uncertain, but one fact may be mentioned here as offering a possible explanation. Gardner and Gainsborough⁸ have shown that the proteins of the blood plasma, especially α -globulin, show a marked affinity for cholesterol, and that removal of the proteins leads to removal of cholesterol with them. In nephritis, particularly the parenchymatous variety, there is a considerable loss of albumin in the urine, which may reasonably be expected to disturb the albumin-globulin ratio of the plasma. This may result in a relative increase of those proteins which show an affinity for cholesterol, and a corresponding increase of cholesterol will appear in the blood. This theory requires investigation.

CHOLESTEROL IN CARDIO-VASCULAR DISORDERS.

The majority of workers agree that the blood cholesterol is raised in arterio-sclerosis, and the question arises as to whether the hypercholesterinaemia is related to the arterio-sclerosis as cause or effect. It must be confessed at once that the experimental work on this subject is as yet inconclusive, but several very interesting observations have been recorded, and may with advantage be considered here.

Anitschkow and Chalutov⁹ were the first to find that atheroma of the aorta could be produced in rabbits by administration of cholesterol dissolved in sunflower oil. The lesions found by these authors consisted of collections of large mononuclear cells loaded with doubly refracting fat and lying beneath the endothelium. The changes corresponded fairly closely with the earlier stages of human atheroma. Similarly, Scarff¹⁰ fed rabbits on a diet containing cholesterol, and found that if the animals were killed after a few months' feeding of this nature there was extensive atheroma of a type comparable with that occurring in human beings—that is, there were collections of large mononuclear cells loaded with fat beneath the endothelium of the vessels. He observed, further, that if the animals were killed some months after the cholesterol feeding had been discontinued, the lesions resembled very closely the later stages of human atheroma, as there was fibrosis of the superficial layers and necrosis of the deeper layers of the vessel wall. Frequently, also, there were crystalline deposits of cholesterol, and splitting of the internal elastic lamella.

Various workers have attempted to reproduce these effects in carnivorous animals, but so far without success. Thus the necessary link between human arterio-sclerosis and that produced experimentally in rabbits is missing. Nevertheless, the association between the two conditions is so striking that the matter must still be left open.

A case reported by Letulle, Labbé, and Heitz¹¹ illustrates well the clinical association between arterio-sclerosis and hypercholesterinaemia. The arterio-sclerosis was shown to develop in a series of exacerbations, each of which was accompanied by a further rise in blood cholesterol. The exact relationship, however, must still remain *sub judice*.

Under cardio-vascular diseases it must also be mentioned that no rise of blood cholesterol accompanies the oedema of cardiac failure. This is of importance in helping to distinguish, particularly in so-called cardio-renal cases, between oedema of cardiac and that of renal origin, for as it has been seen, oedema due to renal disease is normally accompanied by hypercholesterinaemia.

CHOLESTEROL IN DIABETES.

The lipaemia which occurs in severe diabetes is a good indication of the severity of the condition, and as the three principal groups of lipoids—fatty acids, lecithin, and cholesterol—are all increased proportionally, the estimation of one of them will suffice to indicate the degree of lipaemia. Cholesterol is the most stable and easily estimated of the three, and its determination, therefore, affords prognostic guidance of importance.

Treatment of diabetes with insulin diminishes the hypercholesterinaemia, and estimations of cholesterol may be a

useful check on the effect of insulin treatment, particularly in cases with marked acidosis. The cause of the hypercholesterinaemia in diabetes is uncertain, but, as I have shown, injections of insulin into the normal rabbit result in a marked decrease in the cholesterol content of the suprarenals.* Thus, if we assume that the suprarenals synthesize cholesterol, its production may be controlled by insulin, and in the absence of an adequate supply of this, such as occurs in diabetes, there will be an uncontrolled production of cholesterol, which will be reflected as an increase in blood cholesterol, whilst the diminution of the hypercholesterinaemia after insulin treatment of diabetes will, on this theory, be due to the inhibited production of cholesterol by the suprarenals.

A practical point arises out of this observation. It has been noted that hypercholesterinaemia may be a factor in producing or aggravating arterio-sclerosis. It is also possible that certain forms of retinitis may be precipitated by its presence. As both of these conditions are common complications of diabetes, it becomes imperative in preventing them to use insulin in such doses that not only the blood sugar, but the blood cholesterol, is kept within normal limits.

CHOLESTEROL IN DISEASES OF THE LIVER AND BILE PASSAGES.

In this group jaundice and gall-stones are the two principal conditions in which variation of cholesterol metabolism is found.

In jaundice due to obstructive lesions there is usually an increase in blood cholesterol roughly proportionate to the intensity of the jaundice, and due, presumably, to the diminished excretion of cholesterol via the bile. This hypercholesterinaemia may serve to distinguish obstructive from haemolytic forms of jaundice, for in the latter there is often a decrease in blood cholesterol. This is seen, for example, in acholuric familial jaundice and in pernicious anaemia, and may be partly accounted for by the concurrent anaemia.

Cholelithiasis early attracted cholesterol workers, because of the almost constant presence of cholesterol in gall-stones, and repeated efforts have been made to show that these stones form as a deposit of cholesterol from blood overcharged with this substance. Thus, Henes¹² and other workers found hypercholesterinaemia in all cases of gall-stones without fever, and assume this to be directly responsible for the deposition of stones. Henes even emphasizes the value of hypercholesterinaemia in distinguishing the dyspepsia of cholecystitis from that of other diseases.

Recent observations by Fowweather and Collinson¹³ tend to confirm these findings. They record an increase in the cholesterol concentration of blood and bile in many cases, with an increase of blood calcium in a third of the cases. Usually the cholesterol and calcium were increased in the gall-bladder wall. After cholecystectomy they record a fall in blood cholesterol, where this was previously raised. On these results they postulate "that inflammation of the gall-bladder first leads to obstruction to the outflow of the more or less viscid gall-bladder bile, without any corresponding obstruction to the entry of the thinner bile from the liver. The bile continues to be concentrated in the gall-bladder until it is supersaturated with cholesterol, which it deposits in the form of stones. Further, the concentrated cholesterol solution is partly absorbed through the gall-bladder wall with a resultant hypercholesterinaemia." They also suggest that calcium is deposited in the gall-bladder and forms a nucleus for the stones.

Interesting as these postulates are, the facts on which they are based are not universally agreed. Campbell,¹⁴ for instance, denies that hypercholesterinaemia occurs in gall-stones or cholecystitis unless jaundice be present, and even the figures recorded to show that the cholesterol concentration in the bile in these conditions is greater than normal are of doubtful value, for Fox¹⁵ has shown that the concentration of bile constituents is extremely variable and their estimation difficult. Nevertheless, it is possible, as Blaisdell and Chandler¹⁶ have shown, to produce

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gall-stones experimentally in animals by feeding with cholesterol until a hypercholesterinaemia occurs.

Another factor which appears to be associated with the formation of gall-stones is pregnancy, for gall-stones are undoubtedly common in multiparous women. This factor may act through the disturbance of cholesterol physiology which occurs in pregnancy, since hypercholesterinaemia is often present, and I have recently shown* that in rabbits the cholesterol content of the suprarenals is always greater in does than in bucks, but that during pregnancy the suprarenal cholesterol is depleted.

One other possibility may be considered. If the theory that bile salts are derived from cholesterol should prove correct, any interference with liver function might result in a diminished production of bile salts with a corresponding increase of cholesterol excreted in the bile, and a greater tendency for it to be deposited in the form of stones, either directly from the bile or through the wall of the gall-bladder. This would lay the onus of gall-stone formation on a primary defect in liver function.

To sum up, there seems little doubt from all these facts that the formation of gall-stones is to be attributed to some disturbance in cholesterol metabolism, but the evidence is not sufficient as yet to indicate decisively the nature of this disturbance.

ANAEMIAS.

In pernicious anaemia several authorities have recorded a hypocholesterinaemia, and this is not entirely dependent on the diminished number of red corpuscles—in fact, the blood cholesterol is less in the plasma than in the whole blood.

Pacini¹⁷ considered the low cholesterol values in pernicious anaemia to be a possible cause of the disease, on the ground that haemolysis of the red cells would take place more easily in the absence of the full protective powers of cholesterol. He claimed that inunction with lanoline, which contains a high percentage of cholesterol, was beneficial to the condition. The results, however, were not at all convincing, as the improvement may well have coincided with one of the periods of remission which are common in pernicious anaemia, and, further, the number of cases reported was too small to be of any significance. The majority of workers, however, agree with him in recording low values for the blood cholesterol in this disease. Similarly, in chlorosis and other types of anaemia hypocholesterinaemia is usually found.

In secondary anaemias there is some difference of opinion as to the cholesterol of the blood, some authors recording a hypocholesterinaemia, others no material change. In this connexion it may be noted that extensive haemorrhage, produced experimentally, results in a lipaemia, with its accompanying increase in blood cholesterol, so that it seems probable that the changes in blood cholesterol will vary with the severity of the anaemia and the manner and rapidity of its production. This problem is now being investigated by me. Reference must be made to the interesting work of MacAdam and Shiskin¹⁸ in relation to the anaemias. In addition to their confirmation of the findings of other workers on pernicious anaemia and secondary anaemias, these authors found that in acholuric familial jaundice and splenic anaemia there is a low cholesterol content of the blood, which gradually returns to normal after removal of the spleen. The explanation of this phenomenon is uncertain, but it is interesting to recall the property which the spleen possesses of removing excess of cholesterol from the blood. It is possible that in acholuric jaundice and splenic anaemia the spleen may have this property in an excessive degree, and keep the blood cholesterol at a low level, whilst on removal of the organ a return to normal cholesterol values would be expected.

Another group of cases deserves further investigation—namely, those conditions of splenomegaly which are associated with hypercholesterinaemia, as in the case recorded by Dyke.¹⁹ It is said that Gaucher's disease falls into this class, and various authors have claimed that the histological changes in the spleen characterizing Gaucher's

disease can be reproduced by intravenous injections of cholesterol. Others, however, have denied that the histological changes are similar, and further work is required on this problem. I have recently shown¹ that intravenous injections of cholesterol may increase the size of the spleen to twice or three times its normal size. It is thus easy to understand why the spleen becomes enlarged in conditions of hypercholesterinaemia.

The discussion of cholesterol changes in malignant disease, bacterial infections, and formation of local deposits of cholesterol have been omitted from this abstract:

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FURTHER OBSERVATIONS ON PNEUMOCOCCAL INFECTIONS.*

BY

C. H. WHITTLE, M.A., M.D.CAMB., M.R.C.P.LOND.,
CLINICAL PATHOLOGIST, ADDENBROOKE'S HOSPITAL, CAMBRIDGE.

PRIMARY lobar pneumonia and empyema occurring in previously healthy persons arise from infection with pneumococcal strains of high virulence only. Over 100 strains of pneumococci have now been collected, and the main conclusions reached last year^{1 2} have been confirmed.

The Pneumococcal Types in Relation to Disease.†

The distribution of the serological types in relation to the lesion which they caused is given in Table I. Out of a

TABLE I.—Showing the Types of Pneumococci Associated with Different Lesions (Cambridge, 1924-29.)

Lesion.	Type I.	Type II.	Type III.	Group IV.	Total No.
Lobar pneumonia	7	2	0	2	11
Broncho-pneumonia	2	0	2	1	5
Empyema thoracis	24	4	2	1	31
Terminal pneumonia	0	0	2	2	4
Post-operative pneumonia	0	0	1	2	3
Nasal catarrh	0	1	0	3	4
Conjunctivitis	0	1	1	3	5
Bronchitis	0	2	2	8	12
Meningitis, together with otitis media and cerebral abscess	9	1	2	1	13
Other lesions, including abscesses, arthritis, peritonitis, etc.	3	0	1	3	7
Total No. of strains	—	—	—	—	95

total of 47 strains recovered from lobar pneumonia, broncho-pneumonia, and empyema, 33, or 70.5 per cent., belong to Type I; 6 strains, or 12.5 per cent., to Type II; 4, or 8.5 per cent., to Type III; and 8.5 per cent. to Group IV. Such minor lesions as nasal catarrh, conjunctivitis, and

* Summary of an investigation: report to the Science Committee of the British Medical Association, 1929.

† The type agglutinating serums used from 1927 onwards were kindly supplied by the Rockefeller Institute, New York. Previous to this I was using Types I and II serums prepared by Dr. R. R. Armstrong, which were, as I showed from time to time, active agglutinators for the homologous American type cocci at the titres employed in the research.

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