ATHEROSCLEROSIS: ITS CAUSATION AND CONTROL*

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During the past 10 years I have drawn attention on a number of occasions to the basic role of thyroid insufficiency in the causation of essential hypertension.[1,2] In the course of my work on this problem I have become increasingly aware of the possibility that thyroid insufficiency, in a slightly different context, is playing an equally important part in the pathogenesis of atherosclerosis.

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Although the possibility had occurred to me some years ago, it is only in the last 2 years that I have given it serious consideration. In 1960, at the 2nd Congress of the Association of Physicians of South Africa, I presented the facts supporting this view. At that time, although the case was strong, it was by no means complete. Since then, however, the main gaps in our knowledge have been filled, and I believe that I am now in a position to give a fairly complete picture of the main factors in the aetiology of this very common disease.

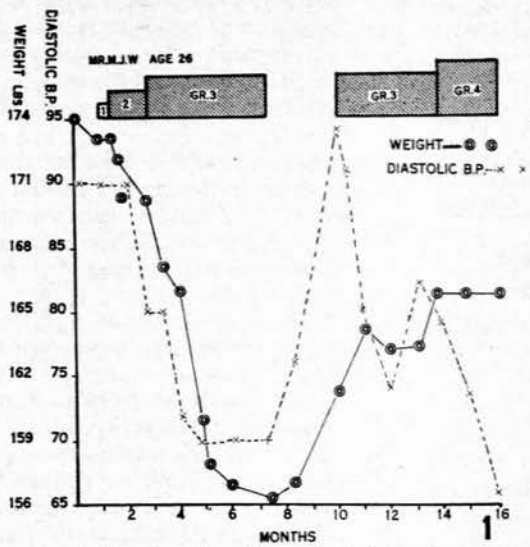
Figs. 1 - 4 and case 1 present clinical evidence of 3 well-recognized effects of thyroid medication: weight loss, fall in the diastolic blood pressure and fall in the serum-cholesterol level.

Case 1

Response of angina pectoris to thyroid medication and dietary restriction.

The patient was Mr. C.H.P., aged 42 years, a married engine-driver.

Diagnosis. Angina of effort for 1 year. During that time, his exercise tolerance was reduced from about 1 mile to about 100 yards.



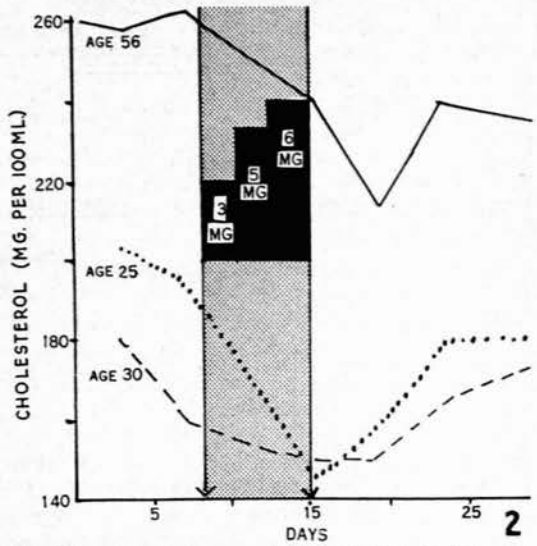


Fig. 1. Showing the effect of administering and withholding thyroid on weight and diastolic blood pressure. Dietetic measures (restriction of fats and starches, and prohibition of sugar) had no effect on the blood pressure and very little on this patient's weight, since he lost only 1 lb. at the end of a month. He was then told to eat what he wished and was given thyroid, with the results indicated.

Fig. 2. Showing the effect of administering and withholding the propionic acid analogue of triiodothyronine on the serum-cholesterol level in 3 subjects aged 56, 20 and 25 years. Desiccated thyroid, thyroxine (dextro- and laevorotatory isomers), propionic and acetic analogues of triiodothyronine, will all produce this effect, though it is claimed that some are more effective than others.

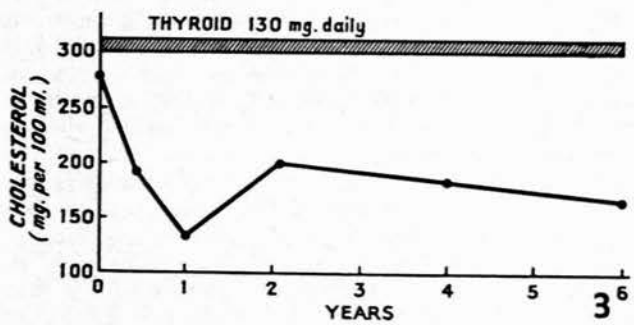
Progress:

Date 1961	*Weight (lb.)*	*Blood pressure*		*Pulse (per min.)*	*Serum cholesterol (mg. per 100 ml.)*	*Thyroid (gr. daily)*
		Systolic (mm. Hg)	*Diastolic (mm. Hg)*			
23 March	180	136	104	82	330	2
22 April	167	124	84	74	275	2½
19 May	153	126	86	74	235	2½
23 June	148	126	86	64	260	3
27 July	149	118	80	68	204	2
22 August	147	118	80	66	260	2

Dietetic measures used were restriction of fats and starches and prohibition of sugar. At the end of the 2nd month exercise tolerance had improved considerably, and at the end of the 3rd month the patient could walk 2 miles without pain.

These facts should be correlated with the findings of the Framingham Study,[3] an epidemiological survey undertaken to measure the risk of coronary heart disease in adult population groups. It is intended that this investigation will continue for a period of 20 years. At the end of 4 years, however, certain interesting results became apparent and an interim report was presented. By then it had become clear that the chances of developing coronary heart disease depended chiefly on the presence of 3 variables: obesity, hypertension and hypercholesterolaemia. In the absence of these, the death rate from coronary heart disease was found to be 10 per 1,000 in 4 years. In the presence of 2 or 3 of these variables the corresponding figure was 143 — a 14-fold increase in risk (Fig. 5).

This decisive result, which established beyond all doubt the prognostic significance of these 3 factors in atherosclerotic heart disease, leads naturally to this question —



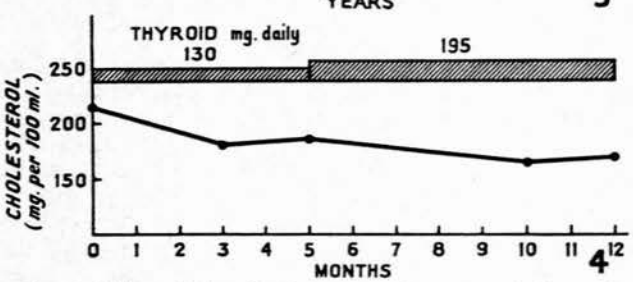


Fig. 3. Effect of thyroid therapy on the serum-cholesterol level (after Barnes).

Fig. 4. Effect of thyroid therapy on the serum-cholesterol level in a patient with myocardial infarction (after Barnes).

is it a mere coincidence that thyroid medication counteracts each of these harmful factors? If we bear in mind the considerable body of evidence linking thyroid insufficiency to atheroma, I would say that it cannot be a coincidence.

Before presenting this evidence I must reiterate that cholesterol metabolism and atheroma are closely and pro-

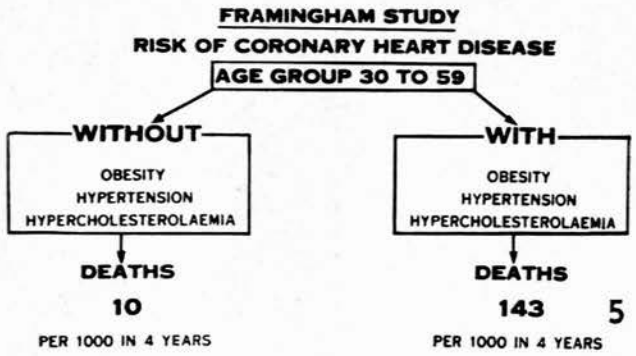


Fig. 5. The Framingham Study. Prognostic significance of obesity, hypertension and hypercholesterolaemia in coronary heart disease.

bably significantly related. I make this assumption because atheromatous vessels contain large amounts of cholesterol and because hypercholesterolaemia is invariably associated with atheroma. Extreme degrees of atheroma are thus the rule in myxoedema, familial hypercholesterolaemia, xanthomatosis and biliary cirrhosis.

THYROID INSUFFICIENCY AND ATHEROSCLEROSIS

I propose to consider the evidence connecting the thyroid with atheroma under 2 headings: experimental and clinical.

A. *Experimental Evidence*

1. In 1913 Anitschov[4] produced hyperlipaemia and atherosclerosis in rabbits by cholesterol feeding. In 1918, 1931 and 1933, independent observations not only confirmed these results, but also showed that when thyroid substance was added to the feeds, atheroma did not occur.[5-7]

2. In 1948 Steiner *et al.*,[8] after failing to produce atheroma in dogs by cholesterol feeding, were able to do so when they depressed the thyroid gland by adding thiouracil to the feeds. In 1900, von Eiselsberg[9] had shown that thyroidectomy caused widespread atheromatosis in sheep and goats — animals which do not normally develop atheroma.

3. In work published in 1959, Deming and Daly[10] drew attention to the relationship between hypertension and atheroma in a neat experiment. By feeding albino rats a high cholesterol diet *plus thiouracil,* they produced atheroma at the base of the aorta and the coronary arteries. Experimental hypertension was then induced and it was found that the hypertensive rats had more atherosclerosis than the normotensive rats on the same atherogenic diet. They also found a positive correlation between the blood pressure and the extent of the atherosclerosis.

B. *Clinical Evidence*

1. Low levels of serum cholesterol are the rule in hyperthyroidism. Conversely, very high levels are found in myxoedema, where extreme degrees of atheroma are also encountered. In hyperthyroidism, atheroma is absent.[11]

2. Thyroxine and its analogues have all been shown to lower the serum-cholesterol level. They achieve this by increasing the rate at which cholesterol is broken down, as is shown by the increased excretion of total bile acids.[12]

3. The serum-cholesterol level is elevated in groups of middle-aged men who have had coronary thrombosis, when compared with coronary-disease-free control groups.[13] Thyroid has been shown to lower the serum-cholesterol level in patients who have had myocardial infarction.[11]

4. Women are relatively immune to coronary thrombosis during the childbearing period. This is usually attributed to the direct effect of oestrogens on cholesterol metabolism, but is more likely to be an indirect result of thyroid overactivity. I suggest this explanation because this gland is particularly active in women during the childbearing period. It is a common observation that the thyroid enlarges at puberty, at each menstrual period, and during pregnancy. These observations can be correlated with animal experiments where it has been shown that injection of oestrogenic substances into rats and guinea-pigs is followed by enlargement of the thyroid, while castration is followed by diminution in its size.[14] Finally, myxoedema, predominantly a disease of women, usually appears after the menopause — at a time when a thyroid insufficiency would be expected to follow the deprivation of oestrogen stimulation.

5. In coronary artery disease both the serum-cholesterol and the serum-uric-acid levels are raised.[15] This fact brings to mind the view of older clinicians that gout is an important factor in arteriosclerosis. It also stresses the parallel between the incidence of gout and coronary thrombosis in women. Both disorders, rare before the menopause, are comparatively frequent after it, when it is known that serum-cholesterol and serum-uric-acid levels rise. It is interesting to record that recent work has shown that thyroid and its analogues lower the serum-uric-acid level[16] (Fig. 6).

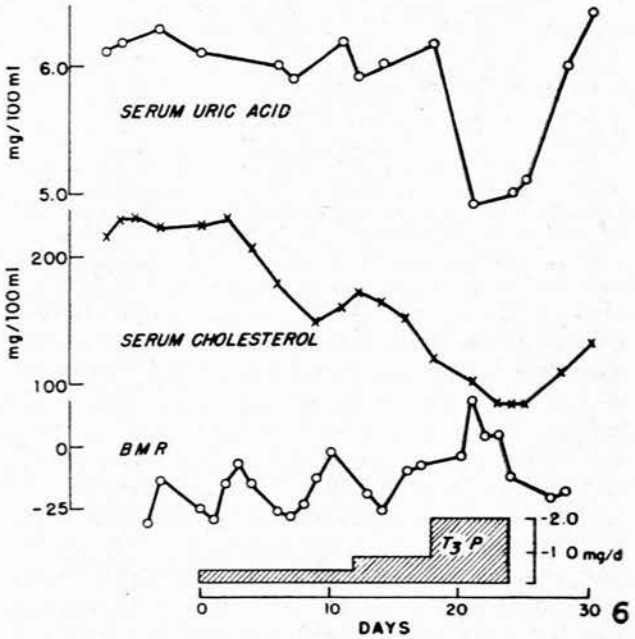


Fig. 6. Effect of increasing doses of triiodothyropropionic acid (T_3P) on the serum-uric-acid and cholesterol levels and on the basal metabolic rate. The patient was receiving a constant repetitive diet (after Leeper *et al.*[16]).

Comment

It may be concluded, then, from the experimental and clinical evidence just considered, that the link between thyroid insufficiency and atheroma is strong. This makes it a reasonable inference that in atherosclerosis we are dealing with a disorder of the endocrine system.

This system, physiologists tell us, is a balanced system. If one hormone lowers blood fats another must be responsible for their elevation. If thyroid is hypolipaemic in action which is the hormone responsible for hyperlipaemia? Recent evidence points clearly and conclusively to adrenaline.

Recognition of this fact has been delayed chiefly because of our preoccupation with the role of nutritional and thrombotic factors in the causation of atherosclerosis. It has also been delayed by the insistence of many physiologists that hyperlipaemia is usually the result of a disturbance in carbohydrate metabolism. This concept is embodied in the old aphorism: 'Fat burns in the flame of carbohydrate'. Only in recent years has the undue emphasis on this factor been corrected by the work of clinicians of the psychosomatic school, who, in a series of interesting experiments, have established the significant role of adrenaline in hyperlipaemia.

ADRENALINE AND HYPERLIPAEMIA

In 1952 Hinkle and Wolf[17] drew attention to a form of response in anxiety which was characterized by restlessness, tachycardia, sweating and *an elevation of blood ketones* (Fig. 7).

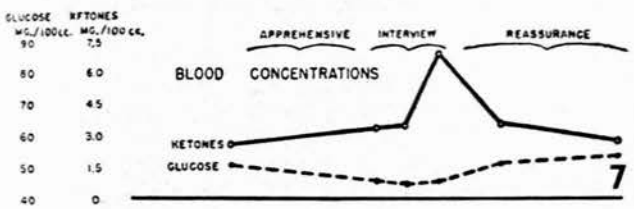


Fig. 7. Effect of emotional stress on blood ketones and blood sugar (after Hinkle and Wolf[17]).

A similar but greater response occurred in many diabetics subjected to similar anxieties. If the stressful situation persisted there occurred in these cases, *after* the rise in blood lipids, a rise in the blood sugar.[18] The tachycardia, the sweating and the hyperglycaemia strongly suggest that the hormone concerned here is adrenaline, because it has long been known that these responses to stress are adrenaline effects.

In 1958 Friedman *et al.*[19] reported hyperlipaemia (cholesterol) and increased coagulability of the blood in accountants immediately preceding the date of tax returns. At times when they were not working under pressure, however, the blood-cholesterol level was lower and the blood-clotting time normal. Increased coagulability of the blood is an adrenaline effect, as Cannon showed many years ago.[20] That this was indeed an adrenaline effect among the accountants was shown by the observation that the more tense among them excreted nearly twice as much adrenaline and noradrenaline as their more composed associates who, by the way, had lower blood-lipid levels.[21]

Finally, Bogdonoff *et al.*[22] measured certain metabolic changes in 20 students undergoing a 15-minute major scholastic examination. They found marked hyperlipaemia (free fatty acid) in all, tachycardia in all, hyperglycaemia in 17 of the 20, increased urinary excretion of adrenaline in all, and *no consistent elevation in noradrenaline*. This last finding is of great interest because it strongly suggests that the hormone involved here is not the hypertensive but the 'metabolic' hormone of the sympathetic nervous system.

This evidence makes it clear that we must now add hyperlipaemia to hyperglycaemia and to hypertension as one of the ways in which the body responds to stressful situations. This conclusion brings to mind certain other interesting relationships linking these 3 stress reactions.

Firstly, the excessive response to stress in each of these 3 ways is associated with a well-known disease — hyperglycaemia with diabetes mellitus, high blood pressure with essential hypertension, and now hyperlipaemia with atherosclerosis. Secondly, these 3 diseases are closely related clinically. Finally, the tendency to react excessively in each of these ways is inherited.

It seems clear, then, that it is those who respond to stress in terms of hyperlipaemia who develop atherosclerosis. We may define this disorder, therefore, as an inherited disturbance of fat metabolism characterized by thyroid insufficiency in relation to adrenaline excess.

COMMENT

It was stated above that delay in recognizing the significant part played by adrenaline in bringing about hyperlipaemia was due to preoccupation with the dietetic and thrombotic factors in atherogenesis. Since a great many workers still believe that these factors play a leading role, and since I believe that this may cause still further delay in instituting correct therapeutic and preventive measures, I now propose to indicate why these factors are not of primary importance.

Dietetic Factors in Atherosclerosis

Nutritional research has made a valuable contribution in establishing that in some way or other the diet of the privileged in Western society is atherogenic. Where, however, it has not proved helpful is in its insistence that an excess or deficiency of one or other constituent of our food is responsible. In this respect 2 factors which have been incriminated are: (1) the excessive ingestion of fat, and (2) the insufficient ingestion of unsaturated fatty acids.

That the excessive ingestion of fat cannot play a leading role in atherogenesis has become apparent from a recent experiment which showed that severe degrees of atheroma could be produced on a fat-free, cholesterol-free diet.[23] This experiment and a number of others with low-fat hypercaloric diets indicate that the important factor is not what is ingested but what the body does with the food. Since the body can convert sugar, starch and protein into fat, the hypercaloric diet, however constituted, would be equivalent to a diet rich in fat. The important dietetic consideration in atherogenesis, then, is far more likely to be an excess of calories than an excess of any particular constituent. In stressing the importance of fat restriction in the treatment and prevention of atheroma, we appear to be at a point in the evolution of the treatment of this

disorder analogous to that at which restriction of sugar and starch was advocated in the treatment of diabetes mellitus. Only when the role of the regulating factor (insulin) was discovered, did the true relationship of diet to diabetes become apparent.

With regard to the claim that the lack of unsaturated fatty acids, such as linoleic acid, is a factor in causation, it should be pointed out that, although these acids lower the serum-cholesterol level, they can play no part in preventing atheroma because they themselves have been recovered in large amounts* from atheromatous lesions of the aorta. Moreover, recent work has shown that as atherosclerosis increases in severity so does the amount of linoleic acid in the atheromatous lesions.[24] Thus, the very substance which it is claimed is helpful is the one which accumulates in increasing amounts as the disease progresses.

The Thrombotic Factor in Atherosclerosis

The view that atheroma follows 'degeneration' of mural thrombi resulting from subintimal haemorrhages, or that it follows the deposition of fibrin on the intimal surface, was first propounded by Rokitansky about 140 years ago. In recent years it has been resuscitated and popularized by Duguid.[25-27] That this cannot be the cause is obvious for these reasons:

1. The experimental work of Anitschov[4] and others on animals and of Wilens[28] on human aortas, showed that atheroma results from the filtration and/or imbibition of cholesterol and other lipids from the plasma.

2. It has recently been shown that 'in lesions of increasing severity (of atherosclerosis), both intimal and medial lipids increase *in a uniform manner*'[29] (my italics).

3. Florey[30] stated: 'It is impossible to derive the amount of lipid present in plaques from breakdown products of red cells or other constituents contained in a thrombus of suitable size'.

4. Recent work has shown that the cholesterol-binding capacity of atherosclerotic intimas is 5 - 7 times greater than that of the normal intima, and that this is due to differences in the globulins of the 2 intimas.[31] This clearly points to some basic biochemical change underlying atheromatosis.

The role of thrombosis in atheroma is best understood if we regard it as the final event in the development of the arteriosclerotic lesion rather than as the first. Slowing of the circulation in a greatly narrowed vessel, ulceration of an atheromatous plaque, or a subintimal haemorrhage in the region of the cholesterol deposit, may all be the immediate precursors of thrombosis. Thrombosis, too, is often initiated by sudden falls in blood pressure associated with shock (haemorrhage, injury, etc.), and by emotional stress. In these conditions the body reacts by secreting increased amounts of adrenaline, a hormone which we know increases the coagulability of the blood.[20] Hyperadrenalinaemia may well be the event which in many cases precipitates thrombosis. Needless to say, this would not occur if the arterial wall had not been previously damaged by cholesterol deposition. We may conclude, then, that thrombosis is only the final event in a progressive pathological process of long standing.

* As cholesterol esters.

Further Factors in Atherosclerosis

The views on the causation of atherosclerosis elaborated above still leave 2 pertinent questions unanswered. They are:

1. Why is it that atheroma is often confined to one group of vessels, such as the coronaries, the cerebral vessels or the peripheral arteries of the lower limbs; in other words why is atherosclerosis patchy in its distribution?

2. Why is it that while hyperlipaemia (hypercholesterolaemia) is always associated with atherosclerosis, atherosclerosis is not always associated with hyperlipaemia?

1. *The localization of lesions in atherosclerosis.* It is generally agreed that atherosclerosis affects vessels chiefly in the region of maximal pressure and increased turbulence of the blood. Some years ago, in attempting to explain the considerable variation normally encountered in the degree and extent of arterial pulsation in the neck, I examined, in cadavers, the 3 large vessels arising from the arch of the aorta. I was surprised to note the wide variation, not only in the site of origin, but also in the *calibre* of these branches. It was pointed out in 1939 by Fishberg[32] that, according to Poiseuille's law, a reduction in the radius of an artery by half brought about a 16-fold increase in the blood pressure. If the large arteries arising from the aorta can be narrower than normal, so can smaller vessels like the coronaries. This would mean that these narrow vessels would be subjected to pressures greatly in excess of the norm and would thus become the seat of atheromatous lesions.

2. *The absence of hyperlipaemia in some cases of atherosclerosis.* Estimations of blood lipids are usually undertaken shortly after a myocardial infarction has supervened. It has recently been shown by Biorck *et al.*[33] and by Dodds and Mills[34] that an acute infarct produces a fall in the serum-cholesterol level. This may take as long as 6 weeks to return to the pre-infarction level. Thus, readings taken during this period are likely to give a false impression. Two other reasons suggest themselves as possible explanations of the discrepancy under consideration. The first is the experimental evidence that even in the absence of hyperlipaemia, lipids tend to be deposited in parts of the intima that have suffered damage. We know that a number of pathological processes unrelated to hyperlipaemia damage the intima — conditions such as syphilis, Buerger's disease, giant-cell arteritis, rheumatic fever, and polyarteritis nodosa and other collagen diseases. Is it not reasonable to suppose that the deposition of lipids in these conditions (and in others we are not aware of) will damage the vessels concerned still further and render the end result indistinguishable from atherosclerosis produced in the usual way? The second fact is the one to which I have already referred, namely, the gross increase in pressure occurring in arteries narrower than normal. The narrowing may be the result of disease or it may be genetically determined. Whatever the cause, I suggest that in these circumstances the filtration effect of the greatly increased blood pressure would be more than equivalent to the effects of hyperlipaemia under normal pressure.

TREATMENT AND PREVENTION OF ATHEROSCLEROSIS

The evidence we have been considering provides an ade-

quate rationale for the treatment and prevention of atherosclerosis. Treatment becomes a question of calorie restriction (say to a maximum of 1,500 calories a day, in which those derived from fat are not excessive) and the careful administration of desiccated thyroid; careful, because many of the patients will have coronary artery narrowing, and too rapid a lowering of the blood pressure would not only make for discomfort, but might even precipitate coronary thrombosis. I suggest that the starting dose in such cases should be ½ gr. daily. This should be increased at weekly intervals by ½ gr. daily until the maintenance dose is decided upon. This would be the maximum dose which the patient can take with comfort. Where coronary artery disease is absent, a bolder course should be adopted.

It is essential that in all cases the pulse rate and the blood pressure be recorded at each visit and that these data be used in the regulation of dosage. Where possible the serum-cholesterol and serum-uric-acid levels should be recorded at approximately 2-monthly intervals. Finally, needless to say, care should be taken to use a thyroid preparation known to be active. There are a number of suitable preparations on the market, where in addition to chemical assay, a bio-assay is required and where an estimation of thyroxine content is also available.

The prevention of atherosclerosis resolves itself into the recognition of those susceptible. The Korean autopsies[35] made it clear that the condition may begin in the third decade of life, if not earlier. Early diagnosis, therefore, is important. I suggest that the following 5 indications might be helpful in detecting the atheroma-prone in the community:

1. A family history of coronary thrombosis, cerebrovascular accidents, peripheral vascular disease and hypertension.

2. Obesity and a tendency to put on weight easily.

3. A diastolic pressure above 90 mm. Hg.

4. A serum-cholesterol level above 200 mg. per 100 ml.

5. A serum-uric-acid level which is elevated (e.g., in women above 4·5 mg. per 100 ml., in men above 5·0 mg. per 100 ml.).

The recognition of these cases will call for considerable skill on the part of the clinician. The diagnosis should not be made lightly, since it will involve a lifetime of supervision and control.

CONCLUSION

It has been said that man is as old as his arteries — a shrewd observation which is largely true. Most deaths and most disabilities of the aged can be traced to a diminution in the blood supply of vital organs brought about by atherosclerosis. Important as it is, however, to pin-point the chief site of senescence, we are no better off if we cannot forestall it.

It seems to me that the evidence we have been considering has suggested how this might be accomplished, for it has shown that the process we have been content to regard merely as the inevitable concomitant of ageing — as the consequence of wear and tear — is in reality a disturbance of endocrine balance which may be remedied.

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