Hormones, Cholesterol, and Coronary Atherosclerosis

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Recent monographs and a rapidly expanding literature\textsuperscript{1-4} indicate the interest and large amount of experimental work on the effects of hormones on lipid metabolism and atherosclerosis. The present paper reviews some of these data not with the purpose of dealing exhaustively with the available information but rather to provide the reader with a digestible summary.

The Thyroid Gland

Myxedema is frequently cited as a condition demonstrating a relation between hormonally induced hypercholesteremia and atherosclerosis. Since this presumed relation has been one of the strongest pillars in the hypercholesteremia theory of atherogenesis, the evidence requires careful evaluation.

A wealth of clinical and human experimental observation indicates a potent influence of the thyroid gland on the metabolism of cholesterol and other lipids. Blood cholesterol, serum phosphatides, and fatty acids are increased in myxedema.\textsuperscript{5,6} In cretinous children, a high ratio of free to total serum cholesterol has been described.\textsuperscript{7} In adults with myxedema, however, normal or increased ester:total cholesterol ratio occurs. The rise in serum cholesterol is greater than that of phospholipid, and the cholesterol:phospholipid ratio is increased.\textsuperscript{8} An increase of low-density (beta) lipoproteins, both in spontaneous and in induced myxedema, is largely in the Sf 0-12 moiety but is found also in fractions Sf 12-400; all of the abnormalities are reversed by the administration of desiccated thyroid.\textsuperscript{9,10} The lipoprotein abnormality may be reversed with very small doses of desiccated thyroid (15 to 30 mg.).\textsuperscript{11}

Similar findings are reported in most animal studies: hypercholesteremia accompanies decreased thyroid function whether this results from surgical extirpation,\textsuperscript{12} \textsuperscript{131} I radiation,\textsuperscript{13} or thiourea administration.\textsuperscript{14} The domestic pig is a notable exception.\textsuperscript{15} The mechanism of the hypercholesteremia has been explained by studies in animals and man.\textsuperscript{16-18} In hyperthyroidism, the serum cholesterol falls in the face of increased cholesterol synthesis, due to increased bile acid excretion (particularly chenodesoxycholic acid). Conversely, in hypothyroidism, cholesterol synthesis is depressed, but bile acid excretion is also decreased; there is a slow turnover of the serum cholesterol, which is elevated apparently because excretion is depressed more than synthesis. Despite the changes in serum cholesterol, available evidence indicates that there is no change in the total body pool of cholesterol in myxedema.

Does myxedema lead to atherosclerosis and is there a relation of the alterations of lipid metabolism in myxedema to atherosclerosis? The evidence is derived from studies of patients with untreated myxedema and cretinism and from studies in experimentally induced hypothyroidism in animals. Since the peak incidence of myxedema occurs at a time when spontaneous atherosclerosis is common, studies attributing atherosclerosis to adult myxedema must be interpreted with caution. Moreover, some of the cases repeatedly cited as evidence for a relation of myxedema to atherosclerosis have been complicated by hypertension and renal disease, conditions which themselves predispose to atherosclerosis.\textsuperscript{19} Of interest in this regard is the classic report of the Committee of the Clinical Society of London based on an extensive investigation of the subject of myxedema.\textsuperscript{20} It noted that "arterial degeneration, indeed, does not appear to

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exist to any unusual extent, at any rate in the larger vessels." Relevant also are our own studies in adults with rheumatic heart disease and severe congestive failure in whom therapeutic total thyroidec-tomy was carried out.21 None of the 8 cases studied by us showed significant coronary atherosclerosis 1 to 13 years after surgical induction of hypothyroidism and its consequent elevated serum cholesterol. Subsequently, careful study with the injection-dissection technic has been made of the hearts of 2 additional patients aged 33 and 45 with multivalvular rheumatic heart disease and chronic congestive heart failure in whom myxedema was induced with I$^{131}$. Again, despite clear hypothyroidism with elevated serum cholesterol for 1 to 4 years, no complete occlusions or significant coronary narrowing was found. It should be noted, however, that these patients received doses (15 to 30 mg.) of desiccated thyroid, which have been shown to alter serum lipoprotein patterns. These data do not disprove a role of cholesterol in the production of human coronary atherosclerosis. They do suggest that the relation of hypothyroidism to adult atherosclerosis requires further documentation.

The finding of a high incidence of atherosclerosis in young patients with hypothyroidism would offer more substantial support for a relation between these conditions. While clear cases have been reported of extensive atherosclerosis in cretins and patients with juvenile myxedema,22 such findings are by no means universal. There have also been reported youthful myxedematous subjects in whom no atherosclerosis existed and, indeed, in whom arteries were described as "delicate."

It would be of great value to know what factors differentiate the fate of those whose vessels were extensively involved and those free of involvement.

While the clinical evidence correlating myxedema, hypercholesteremia, and atherosclerosis is conflicting, experimental evidence in animals is more consistent. Thus, in rabbits, rats, cockerels, and dogs the combination of thyroid depression (as by thiourea) and cholesterol feeding has usually resulted in atherosclerosis. Indeed, in resistant species, such as the rat and the dog, the addition of thiourea to cholesterol feeding is one of the few methods leading to persistent hypercholesteremia and atherosclerosis.24 In cholesterol-fed cockerels, hypothyroidism counteracts the ability of estrogens to inhibit coronary atherogenesis.25 Conversely, thyroid feeding inhibits diet-induced hypercholesteremia and atherosclerosis. Even these experimental data, however, must be regarded with some reservations. Thus, in other studies, feeding thyroid hormones to chicks revealed a conspicuous limitation and inconsistency of its effect. At most hypercholesteremia and atherogenesis were only partially inhibited and in some experiments only minimal effects were noted, despite high dosage. Moreover, large doses of desiccated thyroid inhibited the regression of atherosclerosis that occurs when cholesterol-fed chicks are returned to a plain mash diet. Furthermore, thiourea has been shown to produce more extensive effects than mere thyroid depression; athyreotic thiouracil-treated rats have a higher serum cholesterol than athyreotic controls and liver cholesterol in the former group was 50 per cent higher than in the controls.1 Finally, while hypercholesteremia in excess of 450 mg. per cent for 1 year appears requisite to atherogenesis, similar hypercholesteremia in I$^{131}$ treated dogs not fed cholesterol does not lead to atheroma formation.26

In summary, thyroid depression accompanied by cholesterol feeding will result in marked hypercholesteremia for prolonged periods and atherogenesis in most species. However, mere reduction in thyroid function without cholesterol feeding, yielding only moderate elevation of serum cholesterol, is not a sufficient condition for consistent atherogenesis. Thus, the respective roles of hypothyroidism and hypercholesteremia in atherosclerosis remain to be clarified.

The plasma lipid abnormalities that exist in the hypothyroid state are readily reversed by the administration of thyroid. Significant
depression of serum cholesterol, of the cholesterol phospholipid ratio, and of the beta-lipoprotein cholesterol can be noted even after small doses of thyroid that still leave a hypometabolic state. As a natural extension of this observation, efforts have been made to reduce the cholesterol of euthyroid persons with desiccated thyroid. Unfortunately, large doses of up to 325 mg of thyroid daily are required to produce a persistent reduction in elevated serum lipids.\textsuperscript{27} Such large doses of thyroid are not, however, suitable for administration to patients with coronary disease, euthyroid or hypothyroid, because they may increase metabolic requirements enough to reduce exercise tolerance and provoke angina pectoris. Consequently, an intensive search has been made for a thyroxine derivative that would decrease plasma cholesterol without increasing total body (and particularly cardiac) metabolism. Early enthusiasm for the efficacy of Triac, the acetic acid analogue of triiodothyronine, waned when it was shown to precipitate angina pectoris and diminished exercise tolerance although total body metabolic rate remained unchanged.\textsuperscript{28, 29} Moreover, the fall in plasma cholesterol produced by Triac in euthyroid hypercholesteremic men with coronary disease could not be maintained even with increased dosage. Other thyroactive agents that have been tried experimentally or clinically include the propionic and formic acid derivatives of thyroxine and triiodothyronine. In myxedematous patients and euthyroid patients with hypercholesteremia, administration of triiodothyropionic acid in appropriate dosage reduced serum cholesterol up to 32 per cent with increase of basal metabolic rate of only 4 to 7 per cent.\textsuperscript{30, 31} Investigation of other compounds such as diiodothyroacetic acid (DIAC), 33'5' triiodothyronine, and its derivatives is still in the preliminary stages. Since the chief calorigenic activity of thyroxine exists in its 1-isomer, it has been suggested that a hypocholesteremic effect without metabolic stimulation might be achieved by the use of the d-isomer. At present, d-thyroxine\textsuperscript{32} and d-triiodothyronine are under active study. In appropriate dosage, these agents have some hypocholesteremic effect before elevation of total body metabolic rate. A number of questions, however, remain to be answered with each: 1. In patients with coronary artery disease, is there exacerbation or precipitation of cardiac symptoms with altered cardiac metabolism? 2. What is the degree of reduction of serum cholesterol and does it persist? 3. In the event that a satisfactory answer is found to the first 2 questions, what influence does such a hypocholesteremic effect have on the natural history of atherosclerosis in man?

**Sex Hormones**

While some doubt exists concerning the influence of altered thyroid state on atherogenesis in man, the evidence is more convincing that the sex hormones play a role in the development of arteriosclerosis, particularly of the coronary arteries. There is a higher incidence of angina pectoris and acute myocardial infarction due to coronary disease in men than in women. The early studies of Schlesinger and Zoll\textsuperscript{33} showed a frequency of coronary occlusions in men six times that of women in the age group 40 to 59 and two times in the age group 60 to 79. A larger series of 1,011 consecutive hearts injected, dissected, and x-rayed according to the method of Schlesinger was analyzed by Wessler (personal communication) with respect to the sex and age incidence of coronary artery disease. Approximately 50 per cent of this series had no symptoms referable to the heart, nor was heart disease the cause of death. The percentage of men having complete occlusion of one or more major arteries was twice that of women in the fourth, fifth, and sixth decades but only a third greater in the seventh and eighth decades. An analysis of the incidence of narrowing (where the cross-sectional lumen of the major artery was reduced 50 to 75 per cent) similarly demonstrated a higher frequency in men than in women up to the sixth decade. In the later decades, the incidence in women was equal to that in men.

Several studies have now shown that bilat-
eral oophorectomy in the young woman increases the incidence and severity of coronary artery disease.\textsuperscript{34-37} Wuest et al. compared the degree of coronary atherosclerosis in 49 hearts from women bilaterally oophorectomized 2 to 42 years before death to that in 1,200 hearts from men and women of comparable ages and found significantly more coronary sclerosis in the bilaterally oophorectomized woman than in control women, but less than in the control men. It is interesting that only a small percentage of the women had clinical evidence of coronary artery disease. The small series was not unusually weighted with hypertensive patients nor was there any apparent relation of nutrition to the degree of coronary atherosclerosis. While no unusual increase in clinical incidence of diabetes mellitus was observed, the possibility cannot be completely excluded, since glucose tolerance tests were apparently not carried out.

Rivin and Dimitroff\textsuperscript{35} studied the arteries of patients who died from cancer, some of whom were treated with estrogens or were subjected to bilateral oophorectomy. They found increased atherosclerosis in the castrated female subjects and decreased coronary atherosclerosis in the men treated with estrogen and in the women with hyperestrogenism. A recent study by Oliver and Boyd\textsuperscript{38} of 200 women, who had had a unilateral oophorectomy or hysterectomy with bilateral oophorectomy 20 years before, confirms the influence of bilateral oophorectomy on the development of coronary artery disease. Coronary artery disease had developed in one quarter of the women who had unilateral oophorectomy and in only 1 of 31 patients who had unilateral oophorectomy. An interesting current study in the Bantu provides additional evidence in this regard.\textsuperscript{38} The Bantu has been shown to have a low incidence of death from coronary artery disease.\textsuperscript{39} There is no sex difference in severity of arteriosclerosis or in mortality rate from vascular lesions. It has been observed that the male Bantu has a high estrogen excretion and a high incidence of gynecomastia and cirrhosis of the liver. Moreover, in the Bantu, cholesterol levels are equal in both sexes and do not rise after the age of 30 to 40. Although atherosclerosis is present and may be severe, acute coronary occlusion occurs infrequently.

In western populations, serum cholesterol in the female is lower than in the male until the sixth decade when cholesterol levels become higher than those of the male.\textsuperscript{40} Bilateral oophorectomy results in an elevation of the serum cholesterol and of the cholesterol:phospholipid ratio. Robinson et al. also found an increase in serum lipids after bilateral oophorectomy in patients with overt coronary artery disease.\textsuperscript{41}

With the exception of Engelberg and Glass,\textsuperscript{42, 43} many investigators have now found that estrogen administration results, in both men and women, in a decrease in serum cholesterol, a decreased cholesterol:phospholipid ratio, a decrease in the beta-lipoprotein cholesterol, and an increase in the alpha-lipoprotein cholesterol.\textsuperscript{44-47} The changes in serum cholesterol occur promptly, within 1 or 2 weeks after relatively large doses of estrogen, and are sustained as long as therapy is administered.\textsuperscript{48, 49} As noted above, the phospholipid changes are more marked than the cholesterol changes. As with most agents, the cholesterol fall is greatest in those instances in which initial values are highest. Following cessation of therapy, there may be a rebound. Estrogens are also effective in reducing total and esterified cholesterol, phospholipids, triglycerides, and total lipids in idiopathic hyperlipemias.\textsuperscript{50}

The mechanism of the estrogen effect in decreasing the serum cholesterol has not been elucidated. In some species, estrogen decreases cholesterol biosynthesis, while in others, a stimulating effect is observed. It is known that estrogen increases thyroid activity and may result in an increased serum protein-bound iodine. In pregnancy, however, there is an increase in serum cholesterol rather than a decrease. Another effect of estrogen is to stimulate reticuloendothelial activity,\textsuperscript{51} shown by Friedman, Byers, and Rosenman to have
a significant influence in clearing the blood of cholesterol.\textsuperscript{52}

The protective effects of oral or parenteral estrogens in preventing coronary atheromatosis in cholesterol-fed cockerels has been demonstrated by Katz et al. Estrogens induced the following alterations: feminization, increase in the ratio of free to total plasma cholesterol (FC/TC), enhanced hyperphospholipemia with lowering of the ratio of plasma total cholesterol to lipid phosphorus (C/P) to normal levels, depression of alpha-lipoprotein levels, reduction of \( \text{Sf 20} - 100 + \) levels, and prevention of coronary atherogenesis without influencing formation of aortic lesions.\textsuperscript{3,25} Estrogen also reversed the coronary lesions induced by feeding cholesterol. Androgen prevented the feminization while not affecting the decreased cholesterol: phospholipid ratio induced by estrogens or altering the protection afforded the coronary arteries.

There are striking species differences in the response of serum cholesterol to sex hormones. The female rat has a higher serum cholesterol than the male; cholesterol levels are higher in the pre-estrous to estrous phase and fall off thereafter.\textsuperscript{53} Testosterone lowers the serum cholesterol and other lipids in the female rat. In the male rat, estradiol stimulates cholesterol synthesis and increases serum cholesterol; conversely, testosterone lowers serum cholesterol. Oophorectomy decreases the cholesterolemic response of cholesterol-fed rabbits and rats.\textsuperscript{54} Testosterone lowers serum cholesterol in female rabbits, whereas estrogen therapy of male and female rabbits fed cholesterol caused an exaggerated rise in serum cholesterol.

In view of such species differences, caution must be exercised in the transfer of any of these results to man. The clinical usefulness of estrogen therapy is limited in man by side effects including gynecomastia, decreased libido, and weakness, with histologic evidence of testicular atrophy and fibrosis.\textsuperscript{57,55,56} Moreover, such therapy in men who have already suffered one myocardial infarction does not appear to reduce the incidence of angina pectoris or the frequency of a second acute myocardial infarction, nor does it appear to prolong life. In the postmenopausal woman, estrogen therapy has little effect upon serum cholesterol. Further data are necessary, however, to determine the effects of estrogen on vascular disease in such persons. It thus appears that estrogen therapy should be restricted to the young woman in whom bilateral oophorectomy has been performed.

The search for other substances with hypocholesteremic but less estrogenic effect is under active pursuit. One such substance,\textsuperscript{57} Manvene (a 3,16-substituted estriol derivative) has less estrogenic side effects, but recent reports indicate that this agent alters liver function significantly. A new agent, MER 29, triparanol, related to TACE, a synthetic estrogen, does reduce serum cholesterol and is without estrogenic effect.\textsuperscript{58} It apparently interferes with cholesterol production late in the biosynthetic pathway. An increase in the liver and blood of a cholesterol precursor, 24-dehydrocholesterol or desmosterol, following triparanol therapy has been shown by Avigan et al.\textsuperscript{59} Desmosterol gives a color in the Lieberman-Burchard reaction which is less intense than cholesterol. Consequently, the reduction in total serum sterol is less than would be indicated by the standard methods of cholesterol determination. Whether desmosterol has an effect similar to cholesterol on atherogenesis remains to be determined.

The effects of testosterone and related substances on atherosclerosis in man require additional study. Testosterone does not have a favorable effect on angina pectoris; the initial reports indicating benefit have not been confirmed. Although testosterone produces no change in total serum cholesterol, there is a reduction in alpha-lipoprotein cholesterol and an increase in the beta-lipoprotein cholesterol following testosterone or methyl testosterone. The androgens abolish completely the effects of estrogen on serum cholesterol and lipoproteins in man but have very little effect on the feminizing capacity of estrogens.\textsuperscript{55} A possible
therapeutic effect of derivatives of androgens is suggested, however, by the data of Hellman et al. They have shown a distinct hypocholesterolemic effect following the administration of etiocholanolone and androsterone. Further studies will undoubtedly be forthcoming with these and related substances.

Adrenal Cortex

Evidence of the effects of adrenal cortical hormones on circulating lipid and on the development of atherosclerosis is conflicting. Observations in experimental animals are not in agreement with those obtained in human patients with a variety of pathologic conditions in whom hormones were used for therapeutic purposes. Studies on normal human subjects are limited. Species differences in circulating lipids and lipoproteins limit the applicability of animal experiments to man.

Clinical observation has suggested that hyperfunction of the adrenal cortex (Cushing's syndrome) produces hypercholesteremia and an abnormal distribution of body fat, whereas adrenal cortical insufficiency is associated with a low serum cholesterol and a loss of body fat. Similarly, adrenalectomized dogs maintained on desoxycorticosterone acetate (DOCA) suffer a progressive decrease in plasma phospholipid and cholesterol. The administration of cortisone after DOCA withdrawal has led to a rapid restoration of serum lipids.

However, when either corticotrophin or cortisone acetate was administered intramuscularly to ambulatory men with high plasma cholesterol and coronary artery disease, the plasma cholesterol, the total cholesterol: phospholipid ratio, and beta-lipoprotein cholesterol fell and the alpha-lipoprotein cholesterol rose. Conn and Vogel also showed a drop in serum cholesterol levels during short-term administration of corticotrophin. In contrast, Adlersberg et al. reported that when cortisone was administered to 18 patients severely ill with a variety of clinical conditions, there was an increase of total and esterified cholesterol and phospholipid and a decrease in serum neutral fat. Only 4 of the 18 ill patients had serum cholesterol levels above 250 mg. per cent and, in these, there was no change after cortisone therapy. Bloom and Pierce administered corticotrophin to 9 patients and noted a decrease of serum cholesterol without change in the ester ratio. The effect of cortisone was less consistent. In 6 patients receiving short-term corticotrophin and cortisone therapy and in 8 of 9 patients undergoing long-term cortisone therapy, they noted no trend in Sf 10-20 lipoprotein or serum cholesterol.

In the normal rabbit, administration of corticotrophin and cortisone results in lipemia, increased serum lipoproteins Sf 80-400, and smaller quantities of Sf 40-80. After cessation of cortisone, there is a serial conversion of the larger to smaller lipoprotein until normally occurring Sf 3-12 results. Moreover, the combined administration of cortisone and cholesterol feeding resulted in enhanced levels of all lipid fractions compared with cholesterol feeding alone. In chickens, hydrocortisone and long-acting corticotrophin produced diabetes and enhancement of hypercholesteremia although cortisone was relatively inactive.

Interest in the influence of the adrenal cortex on circulating lipids is enhanced because of the relation of the adrenal cortex to stress. A number of stressful situations (surgery, starvation, infection) in man and animal have been shown to result in a decrease in serum cholesterol. Relief of stress after steroid therapy of serious disease has been suggested as the cause of the resulting rise of cholesterol. On the other hand, an increased serum cholesterol has been shown in medical students at the time of examination and in accountants during tax periods.

The influence of steroids, hypercholesteremia, and stress on human atherogenesis remains obscure. It has been suggested that human beings with hyperadrenocorticism frequently develop premature severe atherosclerosis. If so, the relative role of hypertension, diabetes, and lipids has not been clarified. In the rabbit and chick, the hyperlipemia and
hypercholesteremia occurring after administration of cortisone, hydrocortisone, and corticotrophin has been associated with the deposition of significantly less arterial lipid than in control cholesterol-fed animals. This suggests that in the rabbit other factors (i.e., the state of the ground substance) than hypercholesteremia and its duration exert an influence on atherogenesis. On the other hand, studies in rats suggest that stress may enhance the development of atherosclerosis.

Adrenal Medulla
The effect of stress on serum lipids may be mediated not only through the adrenal cortex but also through the adrenal medulla and the sympathetic nervous system. The effect may be primary or the result of a secondary release brought about by a specific pituitary mobilizing factor.

Norepinephrine and epinephrine increase circulatory levels of free fatty acids in man and in dogs. Prolonged injections of epinephrine result in a rise in serum cholesterol and phospholipid with a smaller and variable response in triglycerides. There is also an increase in the d=1.019 to 1.063 and in the d=1.063 to 1.21 lipoprotein fractions. Both the fatty acid and lipoprotein responses to epinephrine are abolished or markedly reduced in adrenalectomized rats and dogs, and the normal response is restored by cortisone. Thus, increased secretion of both adrenal medullary and cortical hormones may be important in the hypercholesteremia of stress.

Pituitary Gland
Most of the hormones of the pituitary gland exert an effect on lipids through their respective end organs. Thus, the effects of corticotrophin and thyroid-stimulating hormone are considered under the adrenal cortex and thyroid gland. The latter has been shown to have no effect in the myxedematous human. The administration of beef or porcine somatotrophin preparations to man also produces no effect on circulating cholesterol. Recent observations of Seifter and Baeder and by Rudman suggest that fat may be brought into the blood from depots by a pituitary lipid-mobilizing factor separate from the known pituitary hormones.

The effect of pituitary hormones on atherogenesis is unknown. However, in the white female rat, which is notoriously resistant to the development of experimental atherosclerosis, administration of corticotrophin results in explosive atherogenesis, coronary sclerosis, and infarction with lesions strikingly like those seen in man.

Summary
Various hormones have been shown to play an important role in lipid metabolism. Clinical and experimental observations implicate the thyroid, adrenal, gonadal, and pituitary glands in atherogenesis. The evidence is strongest that estrogens play a role in human atherosclerosis. The influence of hypothyroidism requires further study and clarification. Hormones and lipids are obviously not the only factors important in atherogenesis; hypertension, local tissue factors, and altered intravascular coagulation in all probability significantly influence the natural history of the disease.

Summario in Interlingua
Ha esse monistrate que varie hormones ha un rolo importante in le metabolismo de lipidos. Observationes clinie e experimental implica le glandulas thyrroide, adrenal, gonadal, e pituitari in le atherogenese. Le indicios es le plus convincente con respecto al rolo del estrogenos in le genese de atherosclerose human. Le influente de hypothyroidismo require studios additional e debe ancora esser clarificate. Hormones e lipidos es obviemente non le sol factores de importantia in le atherogenese. Hypertension, local factores tissutal, e alteration del coagulation intravascular exerce con alte grades de probabilitate un significative influente super le historia natural del morbo.

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