METABOLIC AND ENDOCRINE ASPECTS OF CORONARY DISEASE

by

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The name arteriosclerosis was first used by Lobstein (1829-1833) to describe hardening of the arteries. It is a generic term for three distinct lesions, which are probably most satisfactorily defined in pathological terms.

**Atherosclerosis**

Atherosclerosis is the name first introduced by Marchand (1904) to describe lesions of the arterial intima, which are characterised by focal thickening and the presence of lipid material in and between the cellular elements. At one extreme there may be marked fibrosis and minimal lipid deposition, and at the other there may be little fibrosis and massive lipid deposition and necrosis; it is from this soft yellow pultaceous material that the disease derives the prefix athero (or, in Greek, athere 

\[\text{αθηρός}\]), meaning mush or gruel. The essential atheromatous/
atheromatous lesion is the fatty and fibrous intimal plaque; these plaques are patchy and irregular and occlude the arterial lumen to a greater or lesser degree. Major and moderate sized vessels are involved, particularly the aorta, the coronary, cerebral and mesenteric arteries.

**Medial Sclerosis**

A different type of arteriosclerosis was described by Mönckeberg (1903). It consists of necrosis and calcification of the media and is not necessarily associated with intimal lesions. Medium sized arteries, such as the arteries of the extremities and the temporal arteries, are most commonly involved; calcification occurs in circular and plate-like masses and cause gross distortion of the arterial wall and the pipe-stem hardening familiar to the clinician.

**Diffuse Arteriolar Sclerosis**

A third type of arteriosclerosis involves small arteries, particularly of the viscera, 100 microns or less in diameter. The lesions are characterised by subintimal hyaline thickening and elastic hyperplasia, and are particularly marked in the renal arteries in association with hypertension.
3.

It is exclusively with atherosclerosis that thesis is concerned. The pleomorphism of atherosclerotic lesions, which range from the purely fibrous to the fatty necrotic deposit, is so remarkable that it is unlikely that any single aetiological concept will explain their derivation. There have been two fundamentally different approaches to the problem of the aetiology of atherosclerosis: one holds that atherosclerosis is the inevitable result of advancing years, and the other postulates that it is an active and potentially reversible process not exclusively associated with age.

The ageing theory of atherogenesis has received support from the fact that the incidence and extent of atherosclerotic lesions increases with age. Atherosclerosis is regarded as an irreversible process which will eventually overcome us all, provided we survive long enough. Moschowitz (1942), in his monograph on vascular sclerosis, concluded "it is hardly likely that any method of therapy will ever be discovered which will restore diseased vessels to their normal texture. Nor can arteriosclerosis be prevented, no more than grey hair or facial wrinkles." Whereas the histological and physico-chemical/
chemical tissue changes which are associated with advancing years undoubtedly contribute to the production of vascular lesions, they do not wholly explain some of the established facts concerning atherosclerosis. Any theory of the genesis of atherosclerosis must provide plausible explanations for the following facts, which will be elaborated during the course of this thesis: atherosclerotic lesions may be absent in advanced age and present in childhood, and they are common in early adult life; atherosclerotic lesions involve the arterial tree in an irregular and patchy distribution; there is a definite relation between the incidence of atherosclerotic lesions with sex and with race; and atherosclerotic lesions can be produced experimentally in various species by differing chemical and physical agents. These observations are most satisfactorily explained by regarding atherosclerosis as an active disease rather than solely as an incurable consequence of ageing.

In general, atherosclerosis involves the abdominal aorta more extensively and earlier than any other vessel, but slight extrusion of intimal plaques have little significant effect on the lumen,
lumen, whereas similar intimal thickening in the coronary or cerebral arteries may cause partial or total occlusion of the lumen. The incidence of atherosclerosis in the coronary arteries is not much less than that of the aorta, but clearly the consequence of coronary atherosclerosis are more disastrous than those of aortic atherosclerosis. It is, therefore, the aetiology of atherosclerosis of the coronary arteries that is the particular subject of this thesis.
THE PURPOSE OF THIS THESIS

The purpose of this thesis is twofold. First, to examine the nature and significance of certain metabolic abnormalities associated with ischaemic heart disease. Second, to propose and expound a thesis that disturbance of the physiological balance of the endocrine glands could contribute to the production of these metabolic abnormalities and to the development of coronary atherosclerosis, and thus be of major importance in the aetiology of ischaemic heart disease.

The thesis is divided into four principle parts. The first part concerns the development of atherosclerosis of the coronary arteries, and the relationship of coronary atherosclerosis to ischaemic heart disease. The second part describes the nature and influences of the circulating lipids and lipoproteins in health, and the abnormalities associated with ischaemic heart disease. The third part contains the exposition of the thesis that an endocrine imbalance could act as an aetiological factor in the development of/
of ischaemic heart disease. The fourth part deals with some of the therapeutic implications of these metabolic and endocrine aspects of coronary disease.
PART I

CORONARY Atherosclerosis AND ISCHAEMIC HEART DISEASE.

A. Atherosclerotic Lesions.

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A. Atherosclerotic Lesions.

1. The early history of hardening of the arteries.

It is now known that aortic atheroma occurred 3,500 years ago. Examination of Egyptian and Coptic mummies, who lived between 1580 B.C. and 525 A.D., revealed extensive patchy atheroma and calcification in the remains of the abdominal and thoracic aortae (Ruffer, 1910, 1911); and Shattock (1909) found calcified atheroma in the aorta of Menephtah, the Pharaoh of the Exodus. Unfortunately examination of these mummies gave no information about the presence of coronary atheroma as the embalming process always entailed removal of the heart. The Egyptians, Greeks and Romans gave little consideration to cardiac pathology, and their knowledge of physiology and anatomy was mostly speculative. Thus there was a gap of many centuries until Bonetus (1678) described in the Sepulchretum the case of a fat middle-aged poet who succumbed in a few minutes after the onset of "distress in breathing": autopsy revealed ossified coronary arteries, which were almost, if not completely, occluded and Bonetus considered that this state of the vessels was responsible for the symptoms. Ossification of the coronary arteries had been reported on a few occasions before Crell wrote at length in 1740 concerning hardening of the coronary arteries. He observed/
He observed that the arterial incrustations were not bony but of a tophaceous nature, and believed that this induration came from the viscid juices of the blood. He considered that these lesions occurred at any age and were not necessarily confined to advanced age. Von Haller (1755), in the course of careful dissection, found a yellow juice between the muscular fibres and the tunica intima of the arterial wall. He considered that this yellow juice gradually hardened and was the cause of ossification of the arteries. This accurate localisation of the site of the atheromatous lesion preceded Virchow's classic work by a hundred years, but it appears to have excited little attention and did not receive confirmation until the following century.

Scarpa (1804) described steatomatous and ulcerative degeneration of the intimal coat of arteries but thought that it was related to lues venera. Subsequently there were several reports incriminating syphilis as a cause of these lesions, and it was not until 1875 that the first accurate histological differentiation between the meso-aortitis of syphilis and the atheromatous intimal lesion was made by Welch. Virchow (1856) emphasised/
emphasised the patchy distribution of atherosclerotic lesions; he described in detail the sites of arterial lesions and considered that local changes in haemodynamics and mechanical forces are important in their production.

Evidence that the coronary arteries are necessary for the maintenance of cardiac function was first provided by Chirac in 1698 when he tied the coronary artery of a dog and observed that soon after the heart had ceased to beat. In 1809 Burns, in a book published in Edinburgh, likened the impairment of the heart's function when the coronary arteries are diseased to the inability of a limb to continue any vigorous action if it has had a ligature placed tightly at its base. He obviously appreciated the importance of adequate blood supply for normal function and believed the blood supply to be impaired by ossified coronary arteries. Hodgson (1815) emphasised the importance of collateral circulation and arteries when the major coronary arteries are atherosclerotic. Hope (1832) recognised that osseous, cartilagenous and steatomatous degeneration of the coronary arteries is associated with loss of their elasticity. Hall (1842) believed that sudden death was often due to arrest of the coronary circulation. He outlined some investigations/
investigations for testing his hypothesis in animals and it was confirmed by Erichsen (1842), who repeated Chirac's original experiment and ligated the coronary arteries in dogs. He recognised that any circumstance that interferes with the passage of blood through the coronary arteries, either directly as in ossification of the coats of those vessels, or indirectly because of a reduction in ventricular output, may cause death.

2. The relation of cholesterol to atherosclerotic lesions.

The name "Cholesterine" was first used by Chevreul (1816) to describe the crystalline substance in gallstones. In 1844, Becquerel and Rodier stated that there is cholesterol in the blood and that it increases with advancing years after the age of 40. Three years later Vogel (1847) showed that the steatomatous arterial degeneration described by Scarpa (1804) is due to deposits of cholesterol; he considered that the presence of these deposits was probably dependent on an excess of cholesterol in the blood. Virchow (1856) also believed that atheromatous lesions resulted from a primary imbibition from the blood, and he did not believe that/
that this was purely passive because an almost neoplastic proliferation of the intimal connective tissue preceded any fatty degeneration and softening. Lipoidal masses in the aorta are doubly retractile because of the presence of cholesterol esters (Mettenheimer, 1857), and the fat content of the aorta increases with the severity of the atherosclerosis (Gazert, 1899). Aschoff (1906) emphasised the great abundance of cholesterol esters in aortic atheroma, and Windaus (1910) undertook for Aschoff the chemical analysis of atheromatous aortae and found that they contain 7 times as much free cholesterol and 20 to 26 times as much ester-cholesterol as normal aortae.

Whereas the presence of cholesterol in the atheromatous lesion had been recognised for a number of years, its significance was not fully appreciated until Anitschkow and Chalatow (1913) succeeded in producing a fairly typical picture of atherosclerosis by feeding rabbits pure cholesterol dissolved in vegetable oil. Since these early experiments atherosclerotic lesions, characterised initially by the presence of fine fat droplets and foam cells in the extracellular ground/
ground substance, have been produced repeatedly in rabbits, dogs and chicks as a result of the addition of cholesterol to the diet. Similar arterial lesions have been produced by the parenteral administration of cholesterol emulsions (Pollak, 1949) and the intravenous administration to normal rabbits of hypercholesterolaemic plasma from cholesterol-fed rabbits (Bradgon, 1952). In the human the lipid composition of atherosclerotic plaques (Buck and Rossiter, 1951) and of the plasma is similar enough to suggest that the lipids of the plaques have their origin in the plasma (Weinhouse and Hirsch, 1940). The oral feeding of tritium-labelled cholesterol to men has resulted in its demonstration in the plasma and subsequently in aortic atherosclerotic plaques (Biggs et al, 1952), and this indicates, therefore, that exogenous cholesterol enters into the metabolism of the atherosclerotic human aorta. In most species the extent and number of cholesterol-induced atherosclerotic lesions is proportional to the degree of hypercholesterolaemia (Anitschkow, 1933; Katz and Stamler, 1953); this does not indicate, however, that preceding hypercholesterolaemia/
15.

hypercholesterolaemia is a sine qua non for the development of typical atheromatous lesions, since such lesions can develop at sites of local anoxia which may favour precipitation of cholesterol in the intima.

3. The relation of blood coagulation to atherosclerotic lesions.

Ideas concerning the formation of fibrin and thrombi were confused and vague until the era of Rokitansky and Virchow. Rokitansky (1841-46) believed that excessive fibrin deposition on the arterial intima leads to intimal/subintimal hypertrophy, atheroma and ossification. Many eminent physicians of the early part of the 19th century considered that fibrin formation and subsequent thrombosis was the result of inflammation of the arterial wall, and Cruveilhier (1849-62) wrote extensively on intravascular clotting and asserted that phlebitis was not only the cause of thrombosis but that it "dominated all pathology". He considered that an arteritis was the foundation of arterial clots, and that the pultaceous matter of atheromatous ulcers was carried by the blood and deposited on arterial walls where inflammation occurred. The subsequent erosions were then repaired by local clotting of the blood. Virchow (1858) was convinced that/
that "inflammation of the blood" was much misunderstood. He studied thrombi and the process of their formation most systematically and stressed the importance of changes in the blood itself, slowing of the circulation and non-inflammatory changes in the vessel wall.

In subsequent years pathologists and physicians were primarily interested in thrombosis as a cause of occlusion of a coronary artery with the resultant acute classical clinical picture. It was not until recently that Duguid (1946, 1949) re-examined Rokitansky's original concept and produced clear-cut evidence that some atherosclerotic lesions result from organisation of fibrin deposits on the intimal surface. Duguid maintains that anoxaemia and fatty degeneration occur deep to the fibrin deposit which becomes covered with endothelium and incorporated into the arterial wall. The degree of narrowing of an atherosclerotic coronary artery is difficult to assess at autopsy for in life the blood pressure tends to iron out excrescences and maintain a smooth intimal lining and full lumen. Indeed, Duguid and Robertson (1955) believe that a vessel which is atherosclerotic is dilated during life and that narrowing of the lumen results/
results from fibrin deposition and thrombosis. There is little doubt that fibrin deposition contributes towards the production of arterial intimal lesions; it is probable, however, that the lesions which depend primarily on fibrin deposition are predominantly fibrous in nature.

4. The coronary circulation and the development of atherosclerotic lesions

Although the aorta is the vessel in which atherosclerosis attains its earliest and most extensive expression (Willius et al, 1933; Albert, 1938), the coronary arteries are far more extensively involved than arteries of corresponding size. Certain characteristics of the coronary circulation may explain this selection.

The relationship between extravascular and intravascular pressure may be important in the development of atherosclerosis. Coronary arteries which penetrate the myocardium are rarely the site of atheroma (Duff and McMillan, 1951; Geiringer, 1951) probably because the extravascular systolic pressure, produced by the contracting myocardium, is equal to or greater than the intravascular pressure; thus there is virtually no passage of lipid material from the lumen/
lumen into the wall of an artery penetrating the myocardium. Furthermore, muscular contraction has the effect of massaging any small amount of lipid material from the site of penetration to a site subject to less violent extravascular pressure, such as the subepicardial arteries. In the subepicardial vessels the lesions are most prominent in the part of the subintimal region nearest to the myocardium (Wolkoff, 1929), possibly because of the greater external movement at this side, but when the artery lies below a bridge of myocardium, the buried portion is said to be more uniformly involved and generally less subject to the disease (Geiringer, 1951), although this observation has recently been contested (Edwards et al, 1956). Subepicardial vessels are commonly the site of atheromatous deposits and generally such deposits occur where intravascular pressure is greatest. When the flow of blood through intramuscular myocardial arteries is more or less arrested in systole, the velocity head in the subepicardial vessels is impeded and the lateral pressure head is augmented. The resultant high lateral systolic pressure against the walls of the subepicardial vessels/
vessels may favour lipid deposition, particularly in vessels supplying the left ventricle. The intramural systolic pressure is lower in the right ventricle and atria, and thus the right coronary and the circumflex branch of the left coronary artery are often less involved than the left anterior descending artery.

There is a definite relationship between the sites of lipid deposition and areas where the uniform blood flow is disturbed (Dock, 1950). The base of the aorta is exposed to rhythmic and violent vibration and frequently has gross athero-sclerotic lesions; the anterior cusp of the mitral valve and the eyelids undergo regular movement and are common sites for lipid deposition. When the intramural portions of the myocardial coronary arteries are more or less occluded during systole, the blood in the subepicardial portion of the arteries undergoes turbulence and thus lipid deposition may be potentiated. Local narrowing, bifurcations and tortuosity are all associated with turbulence of the blood. Disturbance of uniform blood flow can result in instability of the plasma colloidal equilibrium and could favour cholesterol deposition (Hueper, 1945).
The intima of the coronary arteries is developmentally thicker than other arteries and this thickness increases with age (Wolkoff, 1923; Gross et al., 1934). Dock (1946) demonstrated eccentric intimal thickenings in newborn infants and showed that the newborn male coronary intima is $2\frac{1}{2}$ times as thick as that of the newborn female; he thought that these thickenings were developmental irregularities which favoured the subsequent occurrence of atherosclerosis in these areas, although Fangman and Hellwig (1927) concluded that they were early atherosclerotic lesions. These intimal thickenings occur in varying degree in a large number of newborn infants of both sexes, and their distribution resembles that of the adult atherosclerotic lesion (Minkowski, 1947).

5. **Incidence of coronary atherosclerosis.**

Coronary atherosclerosis was not described before the 17th century, yet it is now found almost universally in adult civilised communities. It is difficult to determine how much this represents a true increase in incidence, how much it is a result of the development of anatomical and pathological skill and how much it is due to the/
the increased expectation of life enabling more people to reach an age when coronary atherosclerosis is prevalent. For instance, Morris (1951) concluded, from an analysis of the records of the London Hospital between 1908 and 1949, that there was no increase in the incidence of coronary atheroma in routine autopsies during these 42 years. Although the incidence of atherosclerosis increases with advancing age (Ophüls, 1926), the extent and degree of atherosclerotic lesions are by no means dependent on age. Typical atherosclerotic lesions have been reported from time to time in children and there is no doubt that atherosclerosis of the coronary arteries occurs frequently in young adults. Studies of the coronary arteries of battle casualties in World War I showed atherosclerosis in 11% of youths between 15 and 20 years of age and 23% of men between 25 and 30 (Rüssle, 1919), and in 51% of 652 autopsies performed on men between 17 and 45 (Münckeberg, 1916). Similarly, Enos et al (1953) demonstrated well-marked coronary atherosclerosis in 77% of United States service men killed in action in Korea, and their average age was only 22 years. Conversely, comparatively minimal/
minimal atherosclerosis was observed in one-third of a series of autopsies in patients dying from all causes over the age of 80 (Groddeck, 1939).

Atherosclerotic lesions are present in the coronary arteries in the majority of the adult inhabitants of the civilised communities of the world. Severe and extensive coronary atherosclerosis was reported in 40% of autopsies performed in men between the ages of 40 and 49, and in 75% of the autopsies in men between the ages of 50 and 59 (White et al, 1950). Blumgart (1951) reported complete occlusion, or marked narrowing of one or more major coronary arteries, in 40% of men who died of non-cardiac causes after the age of 40. These estimates refer to extensive atheromatous lesions of the coronary arteries but Friedberg and Horn (1939) showed that myocardial infarction, necrosis and fibrosis can all occur without gross coronary atherosclerosis and occlusion. Intrusion into the lumen of a major coronary artery by one or two comparatively small, but critically placed, atheromatous deposits may be sufficient to reduce the supply of blood below the demands of the myocardium. Such lesions may act as sites for thrombus formation with further luminal narrowing, and, whether or not/
not thrombosis occurs, a few discrete lesions can lead to myocardial infarction. Thus, it is not only the gross and extensive atherosclerotic lesions which are important.

B. CLINICAL FEATURES OF CORONARY ATHEROSCLEROSIS

1. The early history of chest pain, angina pectoris and coronary thrombosis.

From the time of the Egyptian and Greek civilisations it was thought that the heart was immune from disease. This concept was handed down over the centuries and was not seriously questioned until the beginning of the 17th century.

a. Praecordial pain

William Harvey described, probably for the first time, the association of pain in the chest with myocardial disease. He recorded in 1649 the case of "a noble knight, Sir Robert Darcy, when he had reached to about the middle period of life, made frequent complaint of a certain oppressive pain in the chest ('dolore quondam pectoris oppressivo') especially in the night season. The disease became worse and worse and he by and by became cachectic and dropsical, and finally died in one of his severely oppressive paroxysms ('in uno paroxissimo vehementer oppressus'). In his body the wall of the left/
left ventricle of the heart was ruptured, and there was a hole of such size as to admit any of my fingers although the ventricular wall appeared thick and strong". The praecordial pain of coronary disease was first described by Morgagni (1769) in his celebrated "De Sedibus et Causis Morborum". In October 1707 he examined the body of a woman "the mother of a family, who was two-and-forty years of age, had liv'd long in a state of infirm health, and had long been subject to a kind of paroxysm, which appeared in the following manner: on using pretty quick exercise of body, a kind of violent uneasiness came on, within the upper part of the thorax, on the left side, join'd with a difficulty in breathing, and a numbness of the left arm: all of which symptoms soon remitted when these motions ceased". On a journey to Venice in October, 1707 she had just such a paroxysm "and saying that she should die; she actually died on the spot". Extensive irregular hardening and ossification was found throughout the entire length of the aorta. Morgagni described another patient whose symptoms suggested angina and in whom aortic ossification was found. In other cases he described atheromatous lesions, "prominence/
"prominence and pustules", in the coronary arteries. Morgagni himself died from a ruptured ventricle.

b. Angina pectoris

On July 21st 1768, William Heberden read a paper to the Royal College of Physicians in London entitled "Some Account of a Disorder of the Breast". He began "There is a disorder of the breast, marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, of which I do not recollect any mention among medical authors. The seat of it and sense of strangling and anxiety with which it is attended, may make it not improperly be called Angina Pectoris". He described the classical features of angina of effort and also nocturnal attacks lasting for hours. He also described the case of one man who may very well have had a coronary thrombosis; "And I have met with one, in whom it once continued for several days, during all of which time the patient seemed to be in imminent danger of death". Heberden did not recognise that disease of the coronary arteries was the primary factor: "The pulse is................ not disturbed by this pain, and consequently the heart/
heart is not affected by it; which I have had an opportunity of knowing by feeling the pulse, during the paroxysm;"

In 1772 Heberden read a letter which he had received from an unknown sufferer of angina pectoris. He described the subsequent post-mortem which was performed by his friend John Hunter and said "no manifest cause of death could be discovered". In the same year Wall wrote to Hebeden from Worcester and gave an account of the post-mortem examination of a man aged 66, who had had angina. He reported that "the semi-lunar valves, placed at the origin of the aorta, were found to be perfectly ossified". It is interesting that the first case of angina, in which an abnormality was found within the heart, was due to calcific aortic stenosis and that in this case the coronary arteries were possibly not particularly diseased. In 1775 John Hunter describes the post-mortem of a man, who had died in a violent transport of anger and who had previously had angina of effort. "The two coronary arteries, from their origin to many of their ramifications upon the heart, were become one piece of bone". In the following year/
year 1776 Edward Jenner saw John Hunter in Bath, where the latter was convalescing after his second attack of angina pectoris, and wrote a most interesting letter to Heberden; he suggested for the first time the association of disease of the coronary arteries with angina pectoris. He had examined two hearts after death and "in the first I found no material disease of the heart, except that the coronary artery appeared thickened". In the second he "found the same appearance of the coronary arteries as in the former case........ a kind of firm, fleshy tube formed within the vessels, with a considerable quantity of ossific material dispersed irregularly through it. The importance of the coronaries, and how much the heart must suffer from their not being able to perform their functions (we cannot be surprised at the painful spasms), is a subject I need not enlarge upon, therefore I shall just remark that it is possible that all the symptoms may arise from this one circumstance........ Should it be admitted that this is the cause of the disease, I fear that the medical world may seek in vain for a remedy". When John Hunter died in 1793 (17 years after/
after Jenner put forward his hypothesis which was not published for fear that Hunter would read it) his coronary arteries were found to be converted into open bony tubes. By 1802 Heberden was able to report that he had seen nearly 100 patients with angina pectoris; the majority were men near or past 50, but included 3 women and 1 boy aged 12.

At the beginning of the 19th century there were numerous reports of cases of angina pectoris but disease of the coronary arteries was by no means established as a cause. It was variously described as a nervous affliction of the heart or as a consequence of syphilis, and comparatively little attention was given to the conclusions of Jenner and Parry (1799).

Although there were numerous reports of cases of angina during the next 100 years, it was by no means common and it is remarkable that Sir William Osler (1897) saw a total of only 40 cases during all his years of clinical experience. Osler did not see a single case of angina during the ten years of his private and hospital practice in Montreal, and he observed that "it is too narrow a view to suppose the aetiology identical with that of arteriosclerosis. The one is so common/
common and the other comparatively rare". Sir James Mackenzie, with his early experience in general practice and later as a leading cardiologist, wrote as late as 1923 that only 380 patients had consulted him on account of angina pectoris.

c. Coronary thrombosis.

Thrombosis of a coronary artery was confirmed at autopsy, and first diagnosed during life by Hammer (1876), and the first complete and accurate description of myocardial infarction was made in 1880 by Weigert. Welch (1899) emphasised that coronary thrombosis occurred in relation to atherosclerosis of the coronary arteries. In 1910 Obrastzow and Straschesko presented the first complete clinical description of sudden occlusion of a coronary artery; they described three patients, two of whom were diagnosed correctly during life, who had autopsy evidence of a thrombosis of a coronary artery. Two years later Herrick (1912) elaborated the clinical features and indicated for the first time that sudden occlusion of a coronary artery is not necessarily fatal. Despite these reports it was not until about 1920 that coronary thrombosis was seriously considered as/
as an antemortem diagnosis.

2. The incidence of ischaemic heart disease.

In 1920 the crude mortality from ischaemic heart disease (see foot of page) was 22 per million living but in 1955 it was 1575 per million living (Registrar-General's Statistical Tables, England and Wales, 1920-1955); this represents a seventy-fold increase (Fig. 1). A series of 3,000 patients suffering from some form of heart disease was assembled in 1925 and has recently been contrasted with a comparable series of 3,000 patients assembled by the same physician in 1950 (White, 1953): the proportion of patients identified as suffering from ischaemic heart disease was 20% in 1925 and 48.5% in 1950. In a careful clinical and epidemiological survey Ryle and Russell (1949) concluded that the increase in the incidence of ischaemic heart disease is real and probably not influenced greatly by changing fashions in death certification, such as the transference of cases from the designations of myocardial and cardiovascular degeneration to that of diseases of the coronary arteries and angina.

Ischaemic heart disease is used to describe the international statistical classification of arteriosclerotic heart disease (420.0), heart disease specified as coronary arteries (420.1) and angina pectoris without specific mention of the coronary arteries (420.2).
Fig. 1. The crude annual death rate from ischaemic heart disease per million persons living in England and Wales from 1920 to 1955.
The number of patients admitted annually with ischaemic heart disease (angina or coronary thrombosis) to the medical wards of the Edinburgh Royal Infirmary has been determined and expressed as a percentage of the total annual medical admissions for all causes; a similar analysis has been made for patients with cerebral vascular disease. The records allowed analysis over the last 20 years and the results are shown in Figs. 2 and 3. Wartime records were not very adequate and are probably inaccurate on account of the moving population and the occupation of part of the hospital by troops. Although this comparative analysis of morbidity rates is limited by the total number of available hospital beds, it suggests that there has been an increase in morbidity from coronary disease considerably in excess of the morbidity from cerebral vascular disease. A similar trend is seen, particularly in men, when the mortality from coronary heart disease and cerebral vascular disease are expressed as a percentage of the total mortality from all causes (Registrar-General's Statistical Tables for Scotland, 1937-1955) (Figs. 4 and 5).

It is hardly conceivable that this increase in the clinical manifestations of coronary atherosclerosis/
Fig. 2. The number of patients with ischaemic heart disease admitted to the medical wards of the Edinburgh Royal Infirmary expressed as a percentage of the total annual medical admissions for all causes.
Fig. 3. The number of patients with cerebral vascular disease admitted to the medical wards of the Edinburgh Royal Infirmary expressed as a percentage of the total annual medical admissions for all causes.
The combined male morbidity (R. I. E.) and mortality (R. G. for Scotland) rates from ischaemic heart disease and cerebral vascular disease since 1937; the broken lines indicate the war years when records were unreliable.
Fig. 5. The combined female morbidity (R. I. E.) and mortality (R. G. for Scotland) rates from ischaemic heart disease and cerebral vascular disease since 1937; the broken lines indicate the war years when records were unreliable.
atherosclerosis is entirely due to improved diagnosis in a population which is living longer, and it is likely that the increase both in morbidity and mortality from ischaemic heart disease represents a real rise in the incidence of the disease during the last 25 or 30 years.

3. Incidence of coronary thrombosis.

The term coronary thrombosis is most commonly used to describe the acute clinical features which accompany myocardial infarction and does not necessarily indicate whether or not there has been thrombotic occlusion of a coronary artery. It has already been indicated that coronary atherosclerosis may not be increasing very greatly, yet the incidence of ischaemic heart disease is rising rapidly. Since thrombosis of a coronary artery is a cause of ischaemic heart disease, it is important to assess its incidence and, in order to do this, it is necessary to differentiate coronary thrombosis from myocardial infarction. Myocardial infarction can occur with and without occlusion of a coronary artery. Occlusion of a coronary artery can be due to the formation of a thrombus within the artery, or due to gradual intrusion into the lumen by an atherosclerotic plaque; this latter type/
type of occlusion may not cause any symptoms during life as its gradual development allows the formation of adequate collateral vascular channels (Blumgart et al., 1941). When there is no occlusion, infarction can follow prolonged myocardial ischaemia resulting from any discrepancy between the blood supply and the metabolic demands of the myocardium. Friedberg and Horn (1939) did not observe occlusion in 31% of 91 cases of myocardial infarction, and by making close transverse sections Master et al. (1944) found occlusion in only 48 of 100 cases of myocardial infarction.

It is probable that only about half the cases of myocardial infarction have recent and occlusive thrombosis of a coronary artery. Yater et al. (1948) examined 450 hearts from United States service men who died from ischaemic heart disease between the ages of 18 and 39 during World War II. All had advanced coronary atherosclerosis and 114 had gross myocardial infarction; in 8 of these there was no occlusion of any coronary artery, in 27 (24%) there was atherosclerotic occlusion only, in 55 (50%) there was thrombotic occlusion only and in the remaining 27 there was both atherosclerotic and thrombotic occlusion. Of the 336 hearts/
hearts without gross myocardial infarction, there were 38 without coronary occlusion, 148 (44%) with atherosclerotic occlusion only, 117 (35%) with thrombotic occlusion only and in the remaining 33 there was both atherosclerotic and thrombotic occlusion. Similarly, Branwood and Montgomery (1956) demonstrated by the use of a rapid and efficient slicing technique that thrombotic occlusion occurred in 21% and that atherosclerotic occlusion occurred in 18% of 61 cases of recent myocardial infarction; thus, the majority of their cases showed no occlusion of a coronary artery. In 26 subjects, who had a previous history of angina and died suddenly, there was gross coronary atherosclerosis but coronary occlusion in only eight; in 5 of these occlusion was due to a recent thrombus, and in the remaining 3 occlusion was due to rupture from softened atheromatous plaques. Many of the recent occlusive thrombi appeared to be of more recent origin than the related myocardial infarct and Branwood and Montgomery have suggested that some occlusive thrombi may develop as a terminal event after the establishment of the myocardial infarct.

Early studies of coronary occlusion seldom differentiated thrombotic from atheromatous occlusion/
occlusion and thus there is no satisfactory measure against which the present incidence of thrombotic occlusion may be contrasted. It is not possible, therefore, to decide whether the increasing incidence of ischaemic heart disease is partly due to an increase in the incidence of coronary thrombosis; all that can be said is that recent occlusive coronary thrombosis probably does not account for much more than half the cases of myocardial infarction.


With the increase in the incidence of ischaemic heart disease, certain interesting features concerning the prevalence and distribution of coronary disease in the community have become apparent.

a. Age distribution.

An analysis has been made of 1,000 consecutive patients, who were admitted to the medical wards of the Edinburgh Royal Infirmary or the cardiac beds of the Western General Hospital, for treatment of a recent myocardial infarct; none of these patients had had a previous myocardial infarct and all had electrocardiographic evidence of myocardial damage. The maximum incidence of acute myocardial infarction/
infarction occurred in men between the ages of 50 and 59, and in women ten years later between the ages of 60 and 69 (Fig. 6 and Table I).

A recent analysis of 7,032 autopsies over 33 years has suggested that the overall frequency of deaths from atherosclerotic heart disease has not changed very greatly, but that there has been an increase in the incidence under the age of 50 (Saphir et al., 1956). In the course of 5 years 237 patients, who developed ischaemic heart disease under the age of 50, have been seen at the Department of Cardiology at but Edinburgh Royal Infirmary; the expression of this figure as a percentage of the total patients does not give any accurate information of the true age distribution of the disease since many of these patients were specially referred to the Department because of the interest of the staff in coronary disease. Furthermore, analysis of the Registrar-General's statistical reports does not offer any certain indication that the disease may be occurring with increasing frequency in younger age groups as it is not possible to allow for the increasing awareness of coronary disease by the medical profession and the whole population.
Fig. 6. The age distribution of 1000 consecutive patients with acute myocardial infarction.
b. Sex distribution.

There is a remarkable difference in the incidence of clinical coronary disease between the sexes. Analysis of the sex distribution of the 1,000 consecutive admissions, referred to in the preceding subsection, has emphasised the male predominance at all ages and the infrequency of the disease in women during their reproductive years (Table I) (Oliver & Boyd, 1955c; Mussaffia & Puddu, 1956).

Table I. Sex and age distribution of 1,000 consecutive patients with recent myocardial infarction.

<table>
<thead>
<tr>
<th>Age</th>
<th>Numbers of cases</th>
<th>Ratio of Men to Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Younger than 35</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>35 - 39</td>
<td>44</td>
<td>3</td>
</tr>
<tr>
<td>40 - 49</td>
<td>188</td>
<td>26</td>
</tr>
<tr>
<td>50 - 59</td>
<td>256</td>
<td>53</td>
</tr>
<tr>
<td>60 - 69</td>
<td>195</td>
<td>86</td>
</tr>
<tr>
<td>Older than 70</td>
<td>68</td>
<td>61</td>
</tr>
</tbody>
</table>

This sex difference is striking in civilised communities, but is much less marked in primitive communities such as the Bantus (Walker et al., 1956), the Navaho Indians and the negroes in the U.S.A. (Weiss & Gray, 1954). It appears that the sex difference is less evident in populations which are relatively free from coronary disease.
There is less difference in the incidence of severe atherosclerotic lesions of the coronary arteries between the sexes when compared with the sex difference in ischaemic heart disease. The ratio of atherosclerotic lesions between men and women under the age of 40 is 4:3 (Lober, 1953), whereas the corresponding ratio for ischaemic heart disease is in the region of 10:1; similarly, there is no significant sex difference with regard to atherosclerotic lesions of the aorta (Boas and Epstein, 1954).

c. Heredity.

There is little doubt that hereditary factors play a part in the production of ischaemic heart disease and a family history can be obtained more often in young patients than in those who are older (Gertler et al, 1953). Comparison of the parental histories was made between 100 patients with ischaemic heart disease and 100 patients with malignant disease of the skin, nose and throat - there is no reported sex limiting influence in the incidence of cancer in these areas. The malignant 'control' group was matched in age and sex to the coronary group. This analysis (Table II) indicates that a history of angina or coronary thrombosis is more common in/
in the parents of patients with ischaemic heart
disease than in the parents of patients with
malignant disease.

Table II. The incidence of coronary disease
in the parents of patients with
ischaemic heart disease.

<table>
<thead>
<tr>
<th>No parental history</th>
<th>Patients with ischaemic heart disease</th>
<th>Patients with malignant disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No parental history</td>
<td>76</td>
<td>90</td>
</tr>
<tr>
<td>One parent with</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>coronary disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both parents with</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>coronary disease</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

A family history of ischaemic heart
disease probably depends partly on the associated
hypercholesterolaemia which occurs more often
and to a greater extent in young subjects of
coronary disease (see page 76); an example of
this association of hypercholesterolaemia with
a family history of ischaemic heart disease is
shown in Fig. 7. Hypercholesterolaemia is often
inherited (Adlersberg et al, 1949) but its mode
of inheritance is not yet understood.

d. **Body build.**
Fig. 7. An example of ischaemic heart disease and hypercholesterolaemia in a family. The figures represent the plasma cholesterol levels in mg%.
d. **Body build.**

Body build is largely determined by hereditary influences (Sheldon *et al.*, 1940). Coronary thrombosis has been reported to be more common in square muscular men tending to fatness (endomorphic mesomorphs) (Phipps, 1936; Gertler *et al.*, 1953). An analysis was made of the somatotypes of 200 consecutive subjects (149 men and 51 women) with symptoms of coronary disease; there was electrocardiographic confirmation of myocardial infarction in 170 and of ischaemia before or after the Master two-step test in 30. This group was contrasted with 200 miscellaneous inpatients who had no history or clinical features of cardiac, renal, hepatic, metabolic or wasting disease; this control group was matched to the coronary group by age and sex. The height:weight ratio, or ponderal index, which is regarded as a useful measure of massiveness, was assessed in these 400 patients (Ponderal Index = \( \frac{\text{Ht in cms.}}{\sqrt[3]{\text{Wt in Kgms.}}} \)) (Sheldon *et al.*, 1940). The results are expressed in Table III. In men with ischaemic heart disease over the age of 40 the ponderal indices differed significantly from the men of corresponding decades in the control group \((P < 0.05)\), but no significant difference was observed in women. These lower values in men with/
Table III. The ponderal indices in 200 patients with ischaemic heart disease and 200 controls. (A ponderal index of <39 indicates endomorphy; 39-43 indicates mesomorphy; >43 indicates ectomorphy).

<table>
<thead>
<tr>
<th>AGE GROUPS</th>
<th>NUMBERS</th>
<th>MEAN AGE</th>
<th>CONTROL GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ponderal Index</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 - 39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40 - 49</td>
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<td></td>
<td></td>
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<td>50 - 59</td>
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<td></td>
<td></td>
<td>60 - 69</td>
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<td></td>
<td></td>
<td></td>
<td>70+</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CORONARY DISEASE GROUP</td>
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<td></td>
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<td>Ponderal Index</td>
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<td>70+</td>
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<th>AGE GROUPS</th>
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<td></td>
<td></td>
<td>Ponderal Index</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WOMEN 30 - 49</td>
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<td></td>
<td>50 - 59</td>
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<td>60 - 69</td>
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<td>70+</td>
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<table>
<thead>
<tr>
<th>AGE GROUPS</th>
<th>NUMBERS</th>
<th>MEAN AGE</th>
<th>CORONARY DISEASE GROUP</th>
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<td>Ponderal Index</td>
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<td>60 - 69</td>
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<td></td>
<td></td>
<td></td>
<td>70+</td>
</tr>
</tbody>
</table>
with coronary disease confirm that ischaemic heart disease occurs more commonly in endomorphic mesomorphs than in ectomorphs: mesomorphy is the component of masculinity, bone mass and angularity of outline and contour; ectomorphy is the component of linearity and elongation, while endomorphy is the component of softness and roundness but not necessarily of fat.

e. Prevalence in disease with abnormal lipid metabolism.

Ischaemic heart disease and severe coronary atherosclerosis both occur commonly and prematurely in association with certain diseases in which there is disturbance of lipid metabolism and a hypercholesterolaemic tendency. In diabetes mellitus the incidence of coronary thrombosis and of coronary atherosclerosis is more than twice normal (see Part III Section B) and atherosclerosis has been regarded as almost universal in diabetes (Barach, 1949). Pronounced hyperlipaemia and hypercholesterolaemia are commonly found in association with diabetes (see Part III, Section C).

Similarly in hypothyroidism the incidence and severity of ischaemic heart disease and coronary atherosclerosis is increased (see Part III Section B) and there is hypercholesterolaemia (see/
(see Part III, Section C). In chronic renal disease and the nephrotic syndrome there is a significant increase in atherosclerosis (Steiner & Domanski, 1942) and there is often gross hypercholesterolaemia (Peters & Man, 1943c). In familial hypercholesterolaemic xanthomatosis, the incidence of coronary atherosclerosis, which is greatly increased, directly parallels the degree of hypercholesterolaemia and occurs prematurely (Adlersberg et al, 1949).

C. CONCLUSION.

Atherosclerotic arterial lesions occurred thousands of years ago and there is no clear evidence that their incidence is increasing; the nature of the coronary circulation predisposes it to the development of atherosclerotic lesions which are present in the vast majority of the adult members of the civilised communities of the world. In contrast, ischaemic heart disease, which was uncommon before this century, accounted for 20% of all the deaths in Britain in 1955 (Registrar-General's Statistical Tables, England and Wales, and Scotland, 1955). There is a striking male predominance, particularly under the age of 50, in the incidence of ischaemic heart disease but this does not apply to the incidence/
incidence of atherosclerotic lesions of the coronary arteries.

It would seem reasonable to conclude from both these observations that some aetiological factors influence the development of ischaemic heart disease without producing any marked change in the incidence of coronary atherosclerosis. It might be suggested that thrombosis is such a factor but at present there is no convincing evidence that coronary thrombosis is on the increase, and there is little doubt that thrombosis can become incorporated into the arterial wall; thus any increase in the incidence of thrombosis would probably be reflected by an increase in atheroma as well. Myocardial infarction rarely occurs spontaneously in any species other than the human and cannot be produced experimentally without traumatic obstruction of a coronary artery. Yet atherosclerosis occurs spontaneously in a number of species, such as the rabbit and fowl, and can be produced experimentally in others by a variety of constraints, of which cholesterol feeding is almost always one: the extent and degree of these/
these atherosclerotic lesions are more or less directly proportional to the hypercholesterolaemia which is induced. Although in animals myocardial infarction and fibrosis do not occur and atheroma of the coronary arteries is often histologically different from the human lesion, information gained from animal investigations should be studied in the human. Since cholesterol feeding is almost always necessary in order to produce coronary atherosclerosis in animals, cholesterol metabolism and particularly the circulating cholesterol requires close examination in relation to coronary atherosclerosis and ischaemic heart disease in the human.
PART II

THE CIRCULATING LIPIDS AND LIPOPROTEINS IN HEALTH AND IN ISCHAEMIC HEART DISEASE.

A. THE CIRCULATING LIPIDS AND LIPOPROTEINS IN HEALTH.

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C. CONCLUSION. 84
Before any consideration of the circulating lipids in relation to coronary disease, their nature and physiological levels will be summarised.

A. THE CIRCULATING LIPIDS AND LIPOPROTEINS IN HEALTH.

1. Definition of the circulating lipids.

a. **Neutral Fat.** These are triglycerides of various saturated and unsaturated fatty acids containing even numbers of carbon atoms. Chylomicrons (Gage and Fish, 1924) are aggregates of neutral fat molecules, which are visible in plasma since they measure approximately 1 micron in diameter, and are largely derived from chyle; they can be used as a measure of fat absorption.

b. **Fatty Acids.** Neutral fats, esterified cholesterol and the compound lipids all contain fatty acids. Fatty acids also circulate in a chemically "free" form although physically bound to certain proteins.

   i. Non-essential fatty acids are mostly saturated and are synthesised from "active acetate" derived from fat, protein and carbohydrate; examples are palmitic ($C_{16}$) and stearic acid ($C_{18}$).

   ii. Essential fatty acids are unsaturated and/
and are not synthesised by the body but must be obtained from the diet. They are principally linoleic, linolenic and arachidonic acids which contain 2, 3 & 4 double bonds respectively. Of the three main circulating lipids, neutral fat, cholesterol and phospholipids (lecithin), the fatty acids of cholesterol esters are the most unsaturated (iodine number = 158: Bloor et al, 1938) and are probably largely of the essential category.

c. Sterols. Cholesterol makes up between 95% and 98% of the circulating sterols but there are also minute quantities of dihydrocholesterol and 7-dehydrocholesterol in circulation. Cholesterol occurs in the plasma in two forms: approximately 30% as "free" cholesterol, when the hydroxyl group is unesterified and therefore can be precipitated by digitonin, and approximately 70% as ester cholesterol when it is esterified with unsaturated fatty acids. Normally circulating cholesterol is always bound to protein whether free or esterified. Sperry (1936) has indicated that the ratio of ester to total cholesterol is remarkably constant.

d. Compound Lipids. Many of these contain phosphorus and all include fatty acids in their structure.
structure. Phospholipids or phosphatides are usually classified into lecithins, cephalin and sphingomyelin. Lecithins contain the base choline and make up approximately 80% of the plasma phospholipids.

2. Definition of the circulating lipoproteins.

For many years the clarity of serum and plasma suggested that its lipid content is stabilised in solution by linkage to protein, and in 1929 Macheboeuf indicated the presence of lipid-protein complexes by his isolation from serum of a substance which contained a reproducible proportion of nitrogen and lipids. It is now generally believed that neutral fat, cholesterol (free and esterified forms) and phospholipids are transported in the circulation combined with one another and with protein in macromolecular complexes called lipoproteins.

The properties and structure of the lipoproteins, and the enzyme systems involved in their interaction, have not yet been defined but they are known to differ in chemical constitution, in solubility, in molecular size and in isoelectric point. Cholesterol and phospholipids are associated with all the protein fractions but by/
by far the greatest concentration is attached to the $\alpha_1$ and $\beta_1$ globulin fractions (Blix et al., 1941), and these two lipid-laden globulins are termed the $\lambda$ and $\beta$ lipoproteins.

Zone electrophoresis (Wieland and Fischer, 1948), which is based on the different rates of migration of the protein fractions in a buffer in an electric field, permits isolation of each protein component of the serum; actual chemical analysis of the serum lipoproteins can be obtained by subsequent elution of cholesterol and phospholipids from the adsorbent which can be starch or more commonly filter-paper (Nikkilä, 1953; Boyd, 1954). Low temperature ethanol fractionation separates lipoproteins according to their physicochemical properties (Russ et al., 1951). The ultracentrifuge produces a force many thousand times that of gravity and large molecules, such as lipoproteins, are induced to undergo flotation or sedimentation according to the relative density of the molecules and the medium. The concentration of these lipoproteins can be determined during ultracentrifugation by a photographic procedure (Gofman et al., 1949; de Lalla & Gofman, 1954); in general, the low density/
density lipoproteins correspond to the \( \beta \)-lipoproteins and the high density lipoproteins to the \( \alpha \)-lipoproteins.

3. The cholesterol:phospholipid (C/P) ratio.

The ratio of the circulating cholesterol to the circulating phospholipids is reasonably constant in health (Peters and Man, 1943a) and there is evidence to indicate that the phospholipids have a stabilising effect on the colloidal dispersion of cholesterol (Boyd, 1937). The degree of visible lipaemia appears to be inversely related to the lecithin content of the serum (Ahrens and Kunkel, 1949), and thus the translucency of the serum is dependent not only on the lipid-protein attachments but also on the ratio of cholesterol to phospholipid within the macromolecule; thus elevation of the C/P ratio is said to favour cholesterol deposition (Ladd et al, 1949). The average cholesterol:phospholipid ratio (C/P ratio) of whole plasma is approximately 0.80 in health (see Table VI) the C/P ratio of the \( \beta \)-lipoproteins (low density lipoproteins) is approximately 1.25 and the C/P ratio of the \( \alpha \)-lipoproteins (high density lipoproteins) is approximately 0.55. Thus it is apparent/
apparent that the C/P ratio of whole plasma is derived from the C/P ratio of the two major groups of lipoproteins and is dependent on the ratio of one lipoprotein to the other.

4. Origin and fate of the circulating cholesterol.

The plasma cholesterol is derived from an exogenous (dietary) and an endogenous (synthetic) source. Dietary cholesterol is absorbed, 70% in an esterified form and 30% in a "free" (or non-esterified) form, and contributes directly to the plasma cholesterol. Isotope techniques have shown that cholesterol is synthesised from acetate (Bloch & Rittenberg, 1942) and that all twenty-seven carbon atoms are derived from acetate (Wuersch, et al, 1952; Cornforth, et al, 1953). Moreover, acetyl coenzyme A (active acetate) has been shown to be involved in cholesterol biosynthesis (Klein & Lipman, 1953; Boyd, 1953) and is a common key intermediate in the metabolic pathways of carbohydrate, protein and fat. Thus, the three chief dietary elements, which are all sources of active acetate, contribute to the endogenous synthesis of cholesterol. 

All/
All animal cells contain cholesterol and tissue slice techniques have shown that many tissues, with the notable exception of brain (Srere et al., 1950), are capable of cholesterol biosynthesis. However, the liver is the only significant source of plasma cholesterol and there is evidence that in some species the testes, spleen, kidney, lung and adrenals, though possessing the mechanism for cholesterol biosynthesis, in fact withdraw and utilise cholesterol from the plasma under physiological conditions (Landon & Greenberg, 1954). Many major plasma constituents including glucose, albumin, fibrinogen and probably & globulins, are now known to originate entirely in the liver, and the plasma and liver can be regarded as different compartments of the same system (Gould, 1951); isotope techniques have indicated that there is a free interchange of cholesterol and of phospholipids between the plasma and the liver (Hahn and Hevesy, 1940; Gould et al, 1951).

Liver cholesterol is excreted into the bile as cholesterol and bile salts (glycocholate), and intestinal cholesterol is partially re-absorbed; biliary excretion and intestinal re-absorption of cholesterol/
cholesterol are important homeostatic mechanisms for the maintenance of a constant level plasma cholesterol. The transference of plasma cholesterol to venous extrahepatic tissues, where the sterol sometimes may be modified into steroid hormones, is probably largely irreversible.

5. Normal levels of the circulating lipids and lipoproteins and the influence of age and sex.

In all the investigations to be reported the plasma total and free cholesterol, hence esterified cholesterol by difference, has been estimated by the Sperry-Schoenheimer digitonin precipitation procedure as modified by Sperry and Webb (1950); the error of this method has been ± 6%. The phosphorus content of a lipid extract of plasma has been determined by the molybdenum blue method of Allen (1940); the error of this method has been ± 5%. The α and β lipoproteins of serum have been separated by a filter-paper zone electrophoresis micro-technique (Boyd, 1954) and followed by serial cholesterol estimations. It has been possible, therefore, to determine the precise quantity of cholesterol in mg% attached to the two major lipoprotein fractions, but for convenience the distribution of cholesterol between the α and β lipoproteins has/
has often been expressed as a percentage of the total cholesterol - thus 30% on the \( \alpha \)-lipoprotein fraction and 70% on the \( \beta \)-lipoprotein fraction, or an \( \alpha : \beta \) lipoprotein ratio of 30:70; the accuracy of this ratio has been \( \pm 3\% \). The normal daily intake of food had no immediate effect on the plasma cholesterol and C/P ratio (Table IV) and thus blood samples have not been taken exclusively in the fasting state. There is a slight and inconstant variation in plasma cholesterol during the 24 hours of the day (Boyd, 1935), but in most, if not in all, healthy persons the plasma cholesterol is maintained at each individual's constitutional level and large deviations do not ordinarily occur (Sperry, 1937).

Table IV. The effect of ordinary meals on the circulating cholesterol and C/P ratio of 12 healthy men.

<table>
<thead>
<tr>
<th></th>
<th>Fasting (8.0 am)</th>
<th>3 hours after breakfast (11.30 a.m)</th>
<th>3 hours after lunch (4.0 p.m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma cholesterol (mg%)</td>
<td>184</td>
<td>187</td>
<td>191</td>
</tr>
<tr>
<td>C/P ratio</td>
<td>0.76</td>
<td>0.78</td>
<td>0.78</td>
</tr>
</tbody>
</table>

a. Infants.
a. Infants.

The plasma cholesterol of newborn infants is low (Sperry, 1936; Boyd, 1936) but rises rapidly within the first ten days of life; analysis of the blood from the umbilical cord of 5 male and 5 female infants is shown in Table V. From the age of one year there is no significant increase in plasma cholesterol until puberty (Kornerup, 1950; Adlersberg et al, 1956) and after puberty subsequent changes depend on sex.

Table V. The mean circulating lipids and lipoproteins of 5 male and 5 female infants at birth (umbilical cord blood)

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma cholesterol (mg%)</td>
<td>55</td>
<td>56</td>
</tr>
<tr>
<td>C/P ratio</td>
<td>0.48</td>
<td>0.51</td>
</tr>
<tr>
<td>$\alpha : \beta$ lipoprotein ratio</td>
<td>35:65</td>
<td>37:63</td>
</tr>
</tbody>
</table>

b. Men.

The circulating lipids have been studied in 200 men of all decades from puberty (Table VI) and the $\alpha : \beta$ lipoprotein ratio has been determined in 75 of these subjects (Table VII).
<table>
<thead>
<tr>
<th>Decades</th>
<th>Numbers</th>
<th>Mean Age</th>
<th>Mean Plasma Cholesterol in mg.%</th>
<th>Range of Plasma Cholesterol</th>
<th>C/P Ratio</th>
<th>Standard Deviation</th>
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<tbody>
<tr>
<td>15 - 19</td>
<td>8</td>
<td>18</td>
<td>142 ± 28</td>
<td>101 - 199</td>
<td>0.75</td>
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<td>-</td>
</tr>
<tr>
<td>20 - 29</td>
<td>24</td>
<td>24</td>
<td>166 ± 24</td>
<td>111 - 208</td>
<td>0.81</td>
<td>+ 0.12</td>
<td>+ 0.12</td>
</tr>
<tr>
<td>30 - 39</td>
<td>24</td>
<td>36</td>
<td>170 ± 33</td>
<td>112 - 226</td>
<td>0.80</td>
<td>+ 0.15</td>
<td>+ 0.15</td>
</tr>
<tr>
<td>40 - 49</td>
<td>24</td>
<td>40</td>
<td>180 ± 30</td>
<td>106 - 230</td>
<td>0.84</td>
<td>+ 0.10</td>
<td>+ 0.10</td>
</tr>
<tr>
<td>50 - 59</td>
<td>12</td>
<td>52</td>
<td>168 ± 42</td>
<td>100 - 284</td>
<td>0.80</td>
<td>+ 0.14</td>
<td>+ 0.14</td>
</tr>
<tr>
<td>60 - 69</td>
<td>12</td>
<td>64</td>
<td>171 ± 34</td>
<td>121 - 212</td>
<td>0.77</td>
<td>+ 0.12</td>
<td>+ 0.12</td>
</tr>
<tr>
<td>70 +</td>
<td>12</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table VI. The mean plasma cholesterol and C/P ratio in 200 apparently healthy men.
Table VII. The mean $\alpha : \beta$ lipoprotein ratio in 75 apparently healthy men.

<table>
<thead>
<tr>
<th>Decades</th>
<th>Numbers</th>
<th>$\alpha : \beta$ lipoprotein Ratio</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - 29</td>
<td>10</td>
<td>29 : 71</td>
<td>± 7.3</td>
</tr>
<tr>
<td>30 - 39</td>
<td>16</td>
<td>26 : 74</td>
<td>± 7.2</td>
</tr>
<tr>
<td>40 - 49</td>
<td>21</td>
<td>23 : 77</td>
<td>± 6.8</td>
</tr>
<tr>
<td>50 - 59</td>
<td>17</td>
<td>20 : 80</td>
<td>± 7.4</td>
</tr>
<tr>
<td>60 - 69</td>
<td>8</td>
<td>19 : 81</td>
<td>-</td>
</tr>
<tr>
<td>70 +</td>
<td>3</td>
<td>22 : 78</td>
<td>-</td>
</tr>
</tbody>
</table>

The subjects of this study were healthy members of the University and hospital staffs or in-patients without evidence of cardiac, renal, hepatic or metabolic disease. The plasma cholesterol and C/P ratio increased from puberty until the age of 30-35 years, but thereafter no further significant increase was observed (Oliver & Boyd, 1953). Most investigators agree that there is a gradual rise in plasma cholesterol with increasing age up until 35 years, but thereafter the pattern is less clear. The results shown in Table VI indicate that the plasma cholesterol does not increase significantly in men over 35 in Britain and confirm similar observations in the United States (Page et al., 1935).
1935; Foldes and Murphy, 1946): recently these results have been confirmed by Adlersberg et al, 1956 and Little et al, 1956. Other investigators have shown an increase in plasma cholesterol with increasing age (Melka, 1927; Keys, 1949; Gertler et al, 1950; Keys et al, 1950; Kornerup, 1950; Russ et al, 1951). However, Keys et al (1950), who observed a steady progression with advancing age in a large series of Minnesotan bank clerks did not observe any rise in a group of Neapolitans (Keys et al, 1952), and suggested that the difference between the two studies might be related to the lower fat intake of the Italians. Apparently inconsistent results may depend partly on racial and environmental influences (see section on race page 65) since many of these studies were conducted in different countries. At all events the rise in cholesterol is not very marked and probably not an obligatory con-
comitant of ageing.

c. Women.

In view of the striking sex difference in the incidence of clinical coronary disease (Page 37), and the relative immunity from coronary disease enjoyed by premenopausal women,
a special study of the circulating lipids and lipoproteins was made in relation to the two physiological activities which occur in women during their reproductive years - the menstrual cycle and pregnancy.

i. The Menstrual Cycle.

There have been very few studies of the circulating lipids in relation to the menstrual cycle and none in which blood samples have been obtained at frequent intervals throughout the cycle. Elevation of the plasma cholesterol immediately before menstruation was reported by Gonalons (1916), by Moynihan (1925) and by Okey and Boyden (1927) who also observed a rise after menstruation.

The plasma cholesterol and C/P ratio were determined in 12 young healthy women, of whom one was amrried and all were nulliparous, and also in 12 young healthy men; these subjects were students, secretaries or laboratory technicians. The mean age of the female group was 22 years and the mean age of the male group was 21 years.

The subjects were instructed in the use of/
of a clinical thermometer, and asked to record their waking oral temperature every morning while still lying in bed. Ovulation was taken as occurring at or just before the point where the temperature begins to rise during the intermenstrual phase (Rubenstein, 1937). Blood samples were taken in the fasting state twice weekly over 5 weeks. It was particularly important to eliminate possible day to day variations in the quantitative analyses, which were therefore performed by making a lipid extract of the plasma immediately after the sample was taken and storing this extract in a sealed glass ampoule in a cool, dark box. When ten samples had been obtained from each individual, all the estimations were made on the same day.

Definite cyclical changes were observed in all 12 women (Fig. 8) (Oliver & Boyd, 1953a). At ovulation there occurred a striking fall in plasma total cholesterol, due entirely to a fall in plasma ester cholesterol, with a rather less marked fall in plasma phospholipids and therefore a fall in the C/P ratio. Whereas in the follicular and luteal phases of the cycle there was a greater increase in plasma total cholesterol than/
Fig. 8. The mean changes in the circulating lipids of 12 healthy young women during the menstrual cycle. The changes in the plasma total and ester cholesterol and in the plasma phospholipids are shown as the percentage deviation from the mean of the entire cycle; the actual values of the C/P ratio are given.

<table>
<thead>
<tr>
<th></th>
<th>Plasma Total Cholesterol</th>
<th>Plasma Ester Cholesterol</th>
<th>Plasma Phospholipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5</td>
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<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Plasma Total Cholesterol
- Plasma Ester Cholesterol
- Plasma Phospholipids
- Total Cholesterol
- Phospholipid Ratio

Days: 0 5 14 28
than in plasma phospholipids, and therefore a relative increase in the C/P ratio. Fig. 9 shows the changes which occurred in a typical young woman. In contrast, there was no regular fluctuation in the circulating lipids in the 12 young healthy men (Fig. 10).

A further group of 12 normal young women were studied and it was found that the distribution of cholesterol between the $\alpha : \beta$ lipoprotein fractions also underwent regular cyclical change. Less cholesterol was attached to the $\beta$-lipoprotein fraction, and thus there was a higher $\alpha : \beta$ ratio at ovulation than at any time during the menstrual cycle (Fig. 11) (Oliver and Boyd, 1955c).

ii. Pregnancy.

The presence of hypercholesterolaemia during pregnancy was first suggested by Becquerel and Rodier in 1845 and first observed by Neumann and Hermann (1911) and by Chauffard et al. (1911). Early studies, which were all made at or just before term, resulted in discordant views on the behaviour of the circulating lipids in advanced pregnancy. Gardner and Gainsborough (1929), who were the first to study the lipids of pregnancy with/
Fig. 9. The changes in the circulating lipids of a typical healthy young woman during the menstrual cycle.
Fig. 10. The mean changes in the circulating lipids of 12 healthy young men over a period of 35 days. The changes in the plasma total and ester cholesterol and in the plasma phospholipids are shown as the percentage deviation from the mean of the period of study; the actual values of the C/P ratio are given.
Fig. 11. The mean changes in the $\alpha : \beta$ lipoprotein ratio of 12 healthy young women during the menstrual cycle. The high ratio at ovulation is due both to an increase in $\alpha$-lipoprotein cholesterol and a decrease in $\beta$-lipoprotein cholesterol.
with the digitonin precipitation procedure, did not consider that there was any consistent elevation of plasma total cholesterol; and Boyd (1934), who reviewed these early studies, considered that the discrepancies were largely a function of the medium analysed (whole blood, red cells, serum or plasma) and concluded that the most important change was a twofold increase in neutral fat but that there was no significant elevation of total cholesterol. During the last 20 years there have been few studies of the circulating lipids in pregnancy and the puerperium and the belief that hypercholesterolaemia prevails in pregnancy has not been firmly established. The majority of investigators have studied the last few weeks of pregnancy or have made their determinations on pooled blood or on different groups of women at each month.

The subjects studied were 12 normal primigravidae between the ages of 18 and 31 years, mean age 24 years. The women, 13 in number, were selected from the Antenatal Clinic of the Royal Simpson Memorial Maternity Pavilion; one was subsequently discarded from the study on account of abortion at the 12th week of her pregnancy. The conditions for the selection were that the women/
women should be primigravid, less than 12 weeks pregnant, anticipating confinement in hospital and obstetrically and medically healthy. All 12 women attended at two-weekly intervals from the 9th week until confinement. Blood samples were taken at the same time of day every 2 weeks and the patient was instructed to avoid food or fluid during the preceding 3 hours. A blood sample was taken during labour, within 12 hours of birth, on the 3rd, 7th and 14th post-partum days, and 6, 12, and 20 weeks after delivery; the last four samples were not taken at any regular time in the day but when the mother found it most convenient to leave her baby.

At no time can an exact relationship be assumed between the supposed week of pregnancy and the actual stage of gestation which has been reached; it was therefore considered, when assembling the results, more accurate to start calculation of the mean values from a defined point, such as birth, than from a supposed one, such as the 9th week. The mean number of days between the specimen taken during labour and the preceding specimen was 8 and thus this latter sample was regarded as representative of the 39th week, and for each earlier sample 2 weeks were/
were deducted. Two of the women were a little uncertain of the date of the first day of their last menstrual period, but it is likely that this variable has been obviated by assuming the gestation period to be 40 weeks and calculating the mean values in retrograde manner as described. The babies weighed between 6 lbs. 1 oz. and 8 lbs. 12 oz. and there were no obvious signs of pre- or post-maturity.

Hypercholesterolaemia developed in all 12 women and was maximal during the third trimester (Fig. 12) (Oliver and Boyd, 1955a). Between the 7th and 8th months the mean plasma total cholesterol was elevated by 50% (P<0.01); ester cholesterol also rose by 50% and free cholesterol by 59%. The mean plasma total cholesterol fell before labour and nearly reached the initial level by the 4th postpartum month (P<0.01). The plasma phospholipids and the C/P ratio increased by 25% (P<0.01) by the 7th and 8th months of pregnancy (Fig. 12), and subsequently fell at labour. The ratio of cholesterol between the α and β lipoprotein fractions also rose significantly (P<0.02) by the 8th month (Fig. 13). By the 20th post-partum week/
The mean changes in the circulating cholesterol and the C/P ratio of 12 healthy young primigravidae during pregnancy and the puerperium.
Fig. 13. The mean changes in the circulating lipoprotein cholesterol of 12 healthy young primigravidae during pregnancy and the puerperium.

(The serum is applied to the filter paper at the point represented by the vertical line and is induced to migrate towards the anode represented by the +.)

Cholesterol attached to the \( \beta \) and \( \alpha \) lipoproteins before, during, and after pregnancy, as determined by filter paper electrophoresis.
week, when all but one of the women had ceased lactation and all had had at least one menstrual period, none of these mean values had quite returned to the levels observed during the first trimester. These slightly higher levels are not statistically significant for this small group, and no attempt was made to relate them to any particular phase of the first post-partum menstrual cycle. The mean increase in weight of the 12 women during pregnancy was $36 \pm 8$ lb. and by the 20th post-partum week it had fallen by $25 \pm 6$ lb; thus the mean weight of the women was $9$ lb. greater 5 months after the pregnancy than it was before the pregnancy. There was no correlation between the weights during the post-partum period and the levels of the circulating lipids. Eight boys and 4 girls were born to the 12 women and there was no relationship between the degree of hypercholesterolaemia in the mother and the sex or the birth weight of the child.

iii. Post-menopausal years.

The circulating lipids have been studied in 75 women from the age of 40 (Table VIII); the subjects were miscellaneous patients who had no evidence of cardiac, renal, hepatic or metabolic disease.
### Table VIII. The mean plasma cholesterol and C/P ratio in 75 apparently healthy women.

<table>
<thead>
<tr>
<th>Decades</th>
<th>Numbers</th>
<th>Mean Age</th>
<th>Plasma Cholesterol mg.%</th>
<th>Standard Deviation</th>
<th>Range of Plasma Cholesterol</th>
<th>C/P Ratio</th>
<th>Standard Deviation</th>
<th>Range of C/P Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 - 49</td>
<td>20</td>
<td>40</td>
<td>184</td>
<td>± 39</td>
<td>103 - 248</td>
<td>0.79</td>
<td>± 0.09</td>
<td>0.66 - 0.94</td>
</tr>
<tr>
<td>50 - 59</td>
<td>20</td>
<td>54</td>
<td>226</td>
<td>± 44</td>
<td>164 - 295</td>
<td>0.91</td>
<td>± 0.11</td>
<td>0.68 - 1.02</td>
</tr>
<tr>
<td>60 - 69</td>
<td>24</td>
<td>63</td>
<td>198</td>
<td>± 42</td>
<td>143 - 292</td>
<td>0.83</td>
<td>± 0.11</td>
<td>0.61 - 0.99</td>
</tr>
<tr>
<td>70 +</td>
<td>11</td>
<td>75</td>
<td>180</td>
<td>± 52</td>
<td>114 - 300</td>
<td>0.79</td>
<td>± 0.09</td>
<td>0.69 - 0.92</td>
</tr>
</tbody>
</table>
disease. No significant difference was observed between the 40-49, 60-69 and over 70 age groups, but the plasma cholesterol and C/P ratio of the 50-59 age group was significantly higher than the other decades (Oliver & Boyd, 1953b). This unexpected observation has recently been confirmed by Adlersberg et al (1956). Explanation of this rise in the plasma lipids in the first postmenopausal decade and of the subsequent fall in later decades is not readily forthcoming, but might be related to the hormonal changes associated with the menopause and the withdrawal of oestrogens at that time (Page 97). These influences of age and sex and the normal cholesterol pattern in the human are shown diagrammatically in Fig. 14.

6. The influence of race.

It is difficult to dissociate the effect of primary racial genetic characteristics from environmental habits, which could be responsible for most of the racial differences in the circulating lipids and lipoproteins. The economic status and standard of living, and the social and religious habits of various races differ widely; these environment factors determine the quantity/
Fig. 14. A diagrammatic representation of the influence of age and sex on the circulating cholesterol in health. The unbroken line represents males and the broken line represents females; P indicates the level of the plasma cholesterol during the last trimester of pregnancy.
quantity and quality of the diet, and so influence the circulating cholesterol levels very considerably. Elaborate epidemiological studies have indicated that there exists a direct relationship between an increase in dietary fat and standard of living with an increase in circulating cholesterol (Keys and Anderson, 1954; Keys et al, 1955; Bronte-Stewart et al, 1955).

7. The influence of diet.
   a. Dietary cholesterol.

   The circulating cholesterol in men is largely independent of dietary cholesterol. Ingestion of excess cholesterol produces only slight and transient elevation of plasma cholesterol (Collen et al, 1949; Keys, 1949), although very large quantities of cholesterol will cause a greater increase in circulating cholesterol (Messinger et al, 1950). Reduction of dietary cholesterol does not produce any significant decrease in plasma cholesterol (Keys et al, 1950).

   b. Dietary fat.

   Diets rich in fat, but not necessarily in cholesterol, are associated with high levels of circulating cholesterol (Widal et al, 1913; Keys et al, 1955). In most civilised countries more/
more than one-third of the total caloric intake is derived from fat and the average cholesterol levels are higher in these countries than in more primitive communities. Reduction of total dietary fat will lower circulating cholesterol (Mellinkoff et al., 1950) and a rice-fruit diet, devoid of cholesterol and fat, produces a substantial fall (Kempner, 1948).

Until recently animal (saturated) and vegetable (unsaturated) fats were regarded as interchangeable so far as their effect on the circulating lipids and lipoproteins was concerned (Hildreth et al., 1950), but now there is accumulating evidence to indicate that the physiological levels may be dependent in part on the relative, if not on the absolute, intake of essential or unsaturated fatty acids. Nutritional studies on vegetarians compared with non-vegetarians have indicated that high plasma cholesterol levels are closely associated with the intake of saturated fatty acids and lack of unsaturated fatty acids (Hardinge and Stare, 1954). The addition of unsaturated vegetable oils to the diet reduces the level of plasma cholesterol/
cholesterol (Kinsell et al., 1952, 1953) and lack of unsaturated fatty acids appears to result in elevation of the plasma cholesterol (Kinsell et al., 1956). However, complete starvation causes mobilisation of fat reserves, lipaemia, increase in the circulating cholesterol, the C/P ratio (Kartin et al., 1944) and an increase in low density lipoproteins (Rubin and Aladjem, 1954).

B. THE CIRCULATING LIPIDS AND LIPOPROTEINS IN PATIENTS WITH ISCHAEMIC HEART DISEASE.

Evidence has been presented earlier that there are large amounts of cholesterol in atherosclerotic arterial lesions and that this lipid is largely, if not entirely, derived from the plasma. Conditions where there is elevation of the circulating cholesterol are associated with a high incidence of atherosclerosis and ischaemic heart disease (see Page 41). It would seem desirable, therefore, to determine whether there is any abnormality in the circulating lipids and lipoproteins in patients who have developed the clinical manifestations of coronary atherosclerosis.

1. Plasma cholesterol and C/P ratio.

Three studies in the United States have suggested that there is elevation of the plasma cholesterol and probably of the C/P ratio in patients/
patients with ischaemic heart disease (Morrison et al., 1948; Gertler et al., 1950; Steiner et al., 1952). A larger study (Oliver and Boyd, 1953b) precisely controlled in respect of age and sex, was undertaken in order to determine the relationship between cholesterol and ischaemic heart disease in Britain where the dietary habits differ slightly from those in the United States.

The subjects were 200 consecutive admissions with ischaemic heart disease and 200 miscellaneous controls. In the coronary disease group, there was electrocardiographic confirmation of myocardial infarction in 170, and of ischaemia before or after the Master two-step test in 30 who presented clinically with angina of effort; any subject who lacked electrocardiographic confirmation of ischaemic heart disease was excluded. Adequate controls were very difficult to obtain from a hospital population, but were carefully selected members of the medical and scientific staff, and from convalescent inpatients, who had no history or clinical features of cardiac, renal, hepatic or metabolic diseases. The coronary disease group was completed first, and the mean age of each decade of both sexes was determined;
determined; the control group was then completed so that the mean age and number of cases in each decade corresponded with the coronary disease group. Blood samples taken during anticoagulant therapy or within five weeks of the occurrence of myocardial infarction have been excluded from the study. All subjects received a light ward or weight-reducing diet.

The levels of the plasma lipids of each group have been contrasted by decades and expressed separately for the sexes; the mean levels and standard errors are shown in Figs. 15 - 18. Fig. 15 shows the mean plasma cholesterol and Fig. 16 the mean plasma C/P ratio in the men, and Table IXa shows the actual values of these means together with the standard deviations and ranges. There was significant elevation of the plasma cholesterol and the C/P ratio in men with coronary disease in all decades and the maximum elevation occurred between the ages of 30 and 39. Fig. 17 represents the mean plasma cholesterol and Fig. 18 the mean C/P ratio in the women, and Table IXb shows the actual values of these means together with the standard deviations and ranges. As for men, there was significant overall/
Fig. 15. The mean plasma cholesterol levels in 149 consecutive male admissions for ischaemic heart disease and in a matched control group; the number of cases in each group for each decade is also shown.
Fig. 16. The mean plasma C/P ratio in 149 consecutive male admissions for ischaemic heart disease and in a matched control group; the number of cases in each group for each decade is also shown.
Table IXa. The circulating lipids in 149 consecutive men with ischaemic heart disease and 149 controls.

<table>
<thead>
<tr>
<th>Decades</th>
<th>Numbers</th>
<th>Mean age</th>
<th>Plasma Cholesterol mg%</th>
<th>Standard Deviation</th>
<th>Range of Plasma Cholesterol</th>
<th>C/P Ratio</th>
<th>Standard Deviation</th>
<th>Range in C/P Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 39</td>
<td>12</td>
<td>36</td>
<td>278</td>
<td>± 64</td>
<td>201 - 428</td>
<td>0.99</td>
<td>± 0.12</td>
<td>0.79 - 1.23</td>
</tr>
<tr>
<td>40 - 49</td>
<td>36</td>
<td>45</td>
<td>243</td>
<td>± 60</td>
<td>132 - 405</td>
<td>0.93</td>
<td>± 0.14</td>
<td>0.58 - 1.16</td>
</tr>
<tr>
<td>50 - 59</td>
<td>52</td>
<td>54</td>
<td>224</td>
<td>± 59</td>
<td>120 - 424</td>
<td>0.90</td>
<td>± 0.12</td>
<td>0.63 - 1.17</td>
</tr>
<tr>
<td>60 - 69</td>
<td>37</td>
<td>64</td>
<td>223</td>
<td>± 57</td>
<td>117 - 430</td>
<td>0.88</td>
<td>± 0.14</td>
<td>0.53 - 1.17</td>
</tr>
<tr>
<td>70 +</td>
<td>12</td>
<td>75</td>
<td>214</td>
<td>± 66</td>
<td>134 - 340</td>
<td>0.91</td>
<td>± 0.14</td>
<td>0.66 - 1.22</td>
</tr>
<tr>
<td>30 - 39</td>
<td>12</td>
<td>36</td>
<td>174</td>
<td>± 22</td>
<td>127 - 206</td>
<td>0.80</td>
<td>± 0.15</td>
<td>0.49 - 0.98</td>
</tr>
<tr>
<td>40 - 49</td>
<td>36</td>
<td>45</td>
<td>180</td>
<td>± 33</td>
<td>110 - 234</td>
<td>0.84</td>
<td>± 0.15</td>
<td>0.52 - 1.16</td>
</tr>
<tr>
<td>50 - 59</td>
<td>52</td>
<td>54</td>
<td>168</td>
<td>± 30</td>
<td>106 - 230</td>
<td>0.82</td>
<td>± 0.10</td>
<td>0.53 - 1.07</td>
</tr>
<tr>
<td>60 - 69</td>
<td>37</td>
<td>64</td>
<td>166</td>
<td>± 42</td>
<td>100 - 265</td>
<td>0.80</td>
<td>± 0.14</td>
<td>0.51 - 1.30</td>
</tr>
<tr>
<td>70 +</td>
<td>12</td>
<td>75</td>
<td>171</td>
<td>± 34</td>
<td>124 - 242</td>
<td>0.77</td>
<td>± 0.12</td>
<td>0.54 - 0.90</td>
</tr>
</tbody>
</table>
The mean plasma cholesterol levels in 51 consecutive female admissions for ischaemic heart disease and in a matched control group; the number of cases in each group for each decade is also shown.
Fig. 18. The mean plasma C/P ratio in 149 consecutive female admissions for ischaemic heart disease and in a matched control group; the number of cases in each group for each decade is also shown.
Table IXb. The circulating lipids in 51 consecutive women with ischaemic heart disease and 51 controls.

<table>
<thead>
<tr>
<th>Decades</th>
<th>Numbers</th>
<th>Mean age</th>
<th>Plasma Cholesterol mg%</th>
<th>Standard Deviation</th>
<th>Range of Plasma Cholesterol</th>
<th>C/P Ratio</th>
<th>Standard Deviation</th>
<th>Range in C/P Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 49</td>
<td>10</td>
<td>42</td>
<td>241</td>
<td>1+</td>
<td>206 - 342</td>
<td>0.91</td>
<td>1+</td>
<td>0.75 - 1.09</td>
</tr>
<tr>
<td>50 - 59</td>
<td>12</td>
<td>54</td>
<td>232</td>
<td>1+</td>
<td>160 - 282</td>
<td>0.90</td>
<td>1+</td>
<td>0.80 - 1.14</td>
</tr>
<tr>
<td>60 - 69</td>
<td>18</td>
<td>64</td>
<td>251</td>
<td>1+</td>
<td>167 - 432</td>
<td>0.93</td>
<td>1+</td>
<td>0.59 - 1.22</td>
</tr>
<tr>
<td>70 +</td>
<td>11</td>
<td>75</td>
<td>239</td>
<td>1+</td>
<td>188 - 360</td>
<td>0.96</td>
<td>1+</td>
<td>0.75 - 1.23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONTROLS GROUP</th>
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<tbody>
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<td>Decades</td>
</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>60 - 69</td>
</tr>
<tr>
<td>70 +</td>
</tr>
</tbody>
</table>
overall elevation of these values in women with coronary disease in all decades except the sixth when the values of the control group and coronary disease group were identical (see Page 65).

In women, there was no hypercholesterolaemia in the earliest decade of the study.

Whereas there was significant elevation of plasma cholesterol and the C/P ratio in the coronary disease group, there was also considerable overlap in the levels of the two groups. Thus, in 19% of the apparently healthy men either the plasma cholesterol was above 205 mg% or the C/P ratio was greater than 0.94 (these figures are the mean values + one standard deviation), and in 4% either the plasma cholesterol was above 239 mg% or the C/P ratio was greater than 1.07 (these figures are the mean values + two standard deviations). Similarly, 29% of the men with coronary disease had either plasma cholesterol levels lower than 205 mg% or C/P ratio levels less than 0.94. However, only 15% of the 48 men with ischaemic heart disease under the age of 50 demonstrated either a low plasma cholesterol or a low C/P ratio. The overlap between the control and coronary groups is further reduced when lipoprotein analysis are included, and under the age/
age of 50 only between 5 and 9% of patients with ischaemic heart disease had entirely normal levels (see Page 79). The most significant elevation in the plasma cholesterol and C/P ratio occurred in men who had developed ischaemic heart disease under the age of 40 (see Page 77). A marked degree of hypercholesterolaemia may favour the premature development of ischaemic heart disease, and exposure to a high plasma cholesterol for a short period may have the same deleterious effect on the coronary arteries that might result from milder and more long-standing elevation.

2. **Serum lipoproteins.**

   a. **In the human.**

   The circulating lipids do not exist free in plasma but are attached to protein; these lipids are almost entirely bound to the α and β globulins and these lipid-protein macromolecules are termed the α and β lipoproteins (see Page 48). It would seem desirable to determine the distribution of cholesterol between these two lipid carriers in patients with heart disease and other conditions associated with hypercholesterolaemia.

   The subjects (who were different from those reported on the preceding pages) were 50 consecutive men.
men with ischaemic heart disease under the age of 50, 50 miscellaneous controls, 4 men and 4 women with xanthoma tuberosum, 3 men and 1 woman with xanthoma tendinosum, and 2 men with "essential hyperlipaemia". The control group, which was matched by age to the coronary group, consisted of members of the medical and scientific staff and convalescent inpatients, who had no history of clinical features of cardiac, renal, hepatic or metabolic disease. In the coronary disease group, there was electrocardiographic confirmation of myocardial infarction in 39 and of ischaemia before or after the Master two-step test in 11 who presented clinically with angina of effort; these men were not receiving any therapy at the time of the estimation and none had had a myocardial infarct within three months of the determinations, which were repeated on all the subjects on several occasions.

The lipoprotein pattern in the coronary disease group and xanthoma group is contrasted with the normal pattern in Fig. 19. The results expressed in Table X indicate that the concentration of cholesterol attached to the $\beta$-lipoprotein fraction is increased in the coronary disease/
Fig. 19. The circulating lipoprotein cholesterol in healthy men, in men with ischaemic heart disease and in 12 patients with xanthomatosis.

(The serum is applied to the filter paper at the point represented by the vertical line and is induced to migrate towards the anode represented by the +).

CHOLESTEROL ATTACHED TO THE \( \beta \) AND \( \alpha \) LIPOPROTEINS AS DETERMINED BY FILTER PAPER ELECTROPHORESIS
Table X. The percentage distribution of cholesterol between the α and β lipoproteins, expressed as the α : β lipoprotein ratio, in 50 consecutive patients with ischaemic heart disease under the age of 50, in a matched control group and in miscellaneous hypercholesterolaemic conditions.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Mean age</th>
<th>Mean α : β lipoprotein ratio</th>
<th>Standard Deviation</th>
<th>Mean Plasma Cholesterol mg%</th>
<th>Mean C/P Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal men</td>
<td>50</td>
<td>41</td>
<td>28:72</td>
<td>±9.8</td>
<td>193</td>
<td>0.82</td>
</tr>
<tr>
<td>Men with coronary sclerosis</td>
<td>50</td>
<td>41</td>
<td>9:91</td>
<td>±6.1</td>
<td>270</td>
<td>1.04</td>
</tr>
<tr>
<td>Xanthoma tuberosum</td>
<td>8</td>
<td>40</td>
<td>7:93</td>
<td>-</td>
<td>394</td>
<td>1.01</td>
</tr>
<tr>
<td>Xanthoma tendinosum</td>
<td>4</td>
<td>35</td>
<td>3:97</td>
<td>-</td>
<td>442</td>
<td>1.20</td>
</tr>
<tr>
<td>&quot;Idiopathic hyperlipaemia&quot;</td>
<td>2</td>
<td>37</td>
<td>1:99</td>
<td>-</td>
<td>330</td>
<td>1.13</td>
</tr>
</tbody>
</table>
disease group when contrasted with the control group, and the concentration of cholesterol attached to the ξ-lipoprotein fraction is correspondingly decreased (Oliver and Boyd, 1955b); this study has been extended to a larger, but uncontrolled, group of patients with ischaemic heart disease under 50 (see Page 77 and Table XII). The men with coronary disease were all comparatively young (mean age 41) and thus the majority exhibited hypercholesterolaemia (see Pages 70 & 77). It is probable that the rather greater increase in the β-lipoprotein cholesterol in the present investigation when compared with studies of older men with ischaemic heart disease (Nikkilä, 1953; Rosenberg et al, 1954) is largely due to this hypercholesterolaemia, and that, whereas the group can fairly be regarded as representative of the young coronary population, it is probably not a cross section of the older coronary population in which marked hypercholesterolaemia is rather less frequent.

b. Species differences in relation to atherosclerosis.

There are marked and interesting differences between the species in the distribution of cholesterol between the serum lipoproteins/
lipoproteins in relation to the development of atherosclerosis (Table XI) (Boyd and Oliver, 1956); and, although not directly related to the investigation of patients with ischaemic heart disease, this comparative study indicates a positive correlation between an increasing concentration of \( \beta \)-lipoprotein cholesterol and the tendency to develop atherosclerosis. In the rat it is difficult to increase the plasma cholesterol by feeding cholesterol or fat, and until recently this species was regarded as immune from atheroma; however, it has now been shown that exposure to cold (1 - 3°C) for 12 months results in hypercholesterolaemia and the development of typical atherosclerotic lesions in the intima of the aorta (Sellers and You, 1956). In the rat the percentage distribution of cholesterol between the \( \alpha \) and \( \beta \) lipoproteins is approximately 90:10. By contrast the corresponding percentage distribution in normal dog plasma is 70:30, and typical atherosclerotic lesions can readily be induced by cholesterol feeding provided thyroid activity is depressed at the same time (Steiner & Kendall, 1946). In the normal rabbit the percentage distribution of cholesterol between the/
Table XI. Increasing concentrations of cholesterol on the $\beta$-lipoproteins, or a low $\alpha:\beta$ lipoprotein ratio, appear to be related to the development of atherosclerotic lesions in different species.

<table>
<thead>
<tr>
<th>Species</th>
<th>Cholesterol mg% (average figure)</th>
<th>Average $\alpha:\beta$ lipoprotein ratio</th>
<th>Atherosclerotic lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary disease</td>
<td>240 +</td>
<td>10 : 90</td>
<td>Spontaneous lesions</td>
</tr>
<tr>
<td>In health</td>
<td>180</td>
<td>25 : 75</td>
<td></td>
</tr>
<tr>
<td>Fowl</td>
<td>70</td>
<td>40 : 60</td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>40</td>
<td>50 : 50</td>
<td>With cholesterol feeding only</td>
</tr>
<tr>
<td>Dog</td>
<td>140</td>
<td>70 : 30</td>
<td>With cholesterol feeding + thyroid depression</td>
</tr>
<tr>
<td>Rat</td>
<td>50</td>
<td>90 : 10</td>
<td>Rarely produced: Exposure to cold for 1 year.</td>
</tr>
</tbody>
</table>
the \( \alpha \) and \( \beta \) lipoproteins is 50:50, and atherosclerotic lesions can easily be induced by moderate cholesterol feeding. Birds most closely resemble the human in that atherosclerosis may develop spontaneously (Dauber, 1944) and the \( \alpha:\beta \) lipoprotein ratio is approximately 40:60. In the human, virtually every adult shows some degree of atheroma in the aorta and there is therefore no strict normal group for study; comparisons of patients and "normals" are actually comparisons between different degrees of severity of atherosclerotic lesions. However, the \( \alpha:\beta \) lipoprotein ratio in a group of healthy men was 28:72 (see Table X) in contrast to 10:90 in men with established coronary disease (Oliver & Boyd, 1955b).

3. The circulating lipids and lipoproteins in young patients with ischaemic heart disease and their significance.

The presence of marked abnormality of the circulating lipids and lipoproteins in young patients with ischaemic heart disease is further emphasised by the study of 237 such patients, who were referred to the Department of Cardiology in the Edinburgh Royal Infirmary during the last 5 years. These patients all had electrocardiographic/
graphic evidence of myocardial infarction or ischaemia, and the results of their lipid and lipoprotein analysis are shown in Table XII.

Table XII. The mean circulating lipids and lipoproteins in patients with ischaemic heart disease under the age of 50.

<table>
<thead>
<tr>
<th></th>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 40-49</td>
<td>40 40-49</td>
</tr>
<tr>
<td>Number of cases</td>
<td>67 125</td>
<td>20 25</td>
</tr>
<tr>
<td>Plasma cholesterol (mg%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>±68 ±41</td>
<td>±114 ±94</td>
</tr>
<tr>
<td>C/P ratio</td>
<td>1.03 1.00</td>
<td>1.15 0.96</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>±0.03 ±0.04</td>
<td>±0.07 ±0.06</td>
</tr>
<tr>
<td>Number of cases</td>
<td>32 36</td>
<td>13 15</td>
</tr>
<tr>
<td>α:β lipoprotein ratio</td>
<td>8:92 *</td>
<td>11:89 *</td>
</tr>
</tbody>
</table>

* The standard deviation of the β-lipoprotein cholesterol, when expressed in mg%, represents a change of ±5% in the α:β lipoprotein ratio.

† The standard deviation of the β-lipoprotein cholesterol, when expressed in mg%, represents a change of ±8% in the α:β lipoprotein ratio.

In 140 healthy subjects of both sexes under the age of 50 the mean plasma cholesterol was/
was 182 ± 38 mg% and the mean C/P ratio was 0.81 ± 0.13, and in 76 similar subjects the mean α/β lipoprotein ratio was 22:78 ± 7. These subjects were carefully selected members of the medical and scientific staff, and convalescent inpatients who had no history or clinical features of cardiac, renal, hepatic or metabolic diseases; their lipid and lipoprotein analyses have been used as controls in some of the studies already mentioned. The addition of one standard deviation to these means increases the plasma cholesterol level to 220 mg%, the C/P ratio to 0.94 and the α/β lipoprotein ratio to 15:85. Regarding these levels as the upper limits of "normal", the percentage of apparently healthy young adults and the percentage of young patients with ischaemic heart disease with "normal" circulating lipids and lipoproteins have been assessed and the results are shown in Table XIII.

Table XIII.
Table XIII. The percentage of apparently healthy young adults and the percentage of young patients with ischaemic heart disease with "normal" circulating lipids and lipoproteins.

<table>
<thead>
<tr>
<th></th>
<th>Under 40 years</th>
<th></th>
<th>40-49 years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Group</td>
<td>Coronary Group</td>
<td>Control Group</td>
<td>Coronary Group</td>
</tr>
<tr>
<td>Number of cases</td>
<td>80</td>
<td>87</td>
<td>60</td>
<td>150</td>
</tr>
<tr>
<td>Plasma cholesterol below 221 mg%</td>
<td>91%</td>
<td>11%</td>
<td>87%</td>
<td>26%</td>
</tr>
<tr>
<td>C/P ratio below 0.95</td>
<td>87%</td>
<td>30%</td>
<td>83%</td>
<td>38%</td>
</tr>
<tr>
<td>Plasma cholesterol below 221 mg% + C/P ratio below 0.95</td>
<td>93%</td>
<td>9%</td>
<td>91%</td>
<td>20%</td>
</tr>
<tr>
<td>Number of cases</td>
<td>44</td>
<td>45</td>
<td>32</td>
<td>51</td>
</tr>
<tr>
<td>(\lambda:\beta) lipoprotein ratio below 16:84</td>
<td>94%</td>
<td>20%</td>
<td>88%</td>
<td>19%</td>
</tr>
<tr>
<td>Plasma cholesterol below 221 mg% + C/P ratio below 0.95 + (\lambda:\beta) lipoprotein ratio below 16:84</td>
<td>96%</td>
<td>5%</td>
<td>90%</td>
<td>9%</td>
</tr>
</tbody>
</table>
Any attempt to divide the control group from the coronary disease group on the basis of their circulating lipids and lipoproteins depends on the arbitrary choice of certain values to represent the upper limits of normality. Several possibilities were investigated but the division based on the addition of one standard deviation to the mean values of the control group resulted in the most significant separation of the groups. This separation is quite impressive under the age of 40 when only about 5% of each group do not conform to the majority; the division of the groups is not so complete between the ages of 40 and 49 and becomes even less with advancing age - for instance, between 60 and 69 years 44% of the coronary group were found to have normal levels of both the plasma cholesterol and the C/P ratio, although only 10% of the control group had abnormal levels.

When preventive treatment for ischaemic heart disease becomes available, it will be necessary to develop methods for screening the apparently healthy population in order to discover those who will later develop the disease. It is likely/
likely that analyses of the circulating lipids and lipoproteins will contribute greatly to such an investigation of the healthy population. It is suggested, moreover, that these analyses are useful and reasonably reliable adjuvants to the diagnosis of coronary disease in young patients.

4. Heparin clearing reaction.

Post-prandial plasma turbidity or lipaemia normally disappears following the intravenous administration of heparin (Hahn, 1943); this action of heparin can only be initiated in vivo. Block et al (1951) reported that a small intravenous injection of heparin produced less clearing of lipaemic plasma in 27 males with myocardial infarction or with atherosclerotic obliteration of the lower limb vessels when compared with 23 normal men of a slightly younger age group. They suggested that there may be a relationship between atherosclerosis and the lack of disappearance of alimentary lipaemia following heparin. It was thought that this observation merited further investigation.

One hundred subjects were studied. With the exception of a few ill patients, 50 were consecutive admissions with electrocardiographic confirmation/
confirmation of myocardial infarction or ischaemia, and 50 were miscellaneous hospital inpatients without evidence of cardiac, hepatic, renal or metabolic diseases. The subjects received for breakfast 100 g. of fat in the form of 40% cream and developed a consistent post-prandial lipaemia. The turbidity of the plasma was measured by determining its optical density (on a Unicam Absorptiometer) before, 3 hours after and $3\frac{1}{2}$ hours after the fat meal. A small intravenous injection (300 I. U.) of heparin was given at the height of the postprandial lipaemia 3 hours after the fat meal.

Heparin induced less clearing of the lipaemia in the coronary disease group than in the control group (Table XIV) (Oliver and Boyd, 1953c). In Fig. 20 the average optical density of each group has been diagrammatically superimposed on the normal absorption curve following the ingestion of 100 g. of fat. Thus, at $3\frac{1}{2}$ hours the change in the translucency of lipaemic plasma resulting from the heparin injection can be contrasted with the level of lipaemia before heparin was administered. The course of normal lipaemia was studied in 20 subjects, and the maximum lipaemia developed/
The mean percentage clearing of lipaemic plasma 15 minutes after heparin.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Mean age</th>
<th>Percentage clearing</th>
<th>Standard Deviation</th>
<th>Range in percentage clearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary group</td>
<td>36</td>
<td>51</td>
<td>30</td>
<td>+24</td>
<td>0 - 84</td>
</tr>
<tr>
<td>Control group</td>
<td>36</td>
<td>51</td>
<td>68</td>
<td>+17</td>
<td>30 - 100</td>
</tr>
<tr>
<td>Coronary group</td>
<td>14</td>
<td>54</td>
<td>35</td>
<td>+21</td>
<td>0 - 76</td>
</tr>
<tr>
<td>Control group</td>
<td>14</td>
<td>54</td>
<td>56</td>
<td>+34</td>
<td>0 - 100</td>
</tr>
</tbody>
</table>

**Probability that the difference in mean percentage clearing is due to change:**

- **Males**  
  - Preheparin optical density - Postheparin optical density
  - Probability = $100 \times \frac{\text{Preheparin optical density} - \text{Postheparin optical density}}{\text{Preheparin optical density}}$

- **Females**  
  - Preheparin optical density - Postheparin optical density
  - Probability = $100 \times \frac{\text{Preheparin optical density} - \text{Postheparin optical density}}{\text{Preheparin optical density}}$

The optical density of the fasting plasma is subtracted from the pre- and post-heparin optical densities before the calculation is made.
Fig. 20. A diagrammatic representation of the clearing of alimentary lipaemia induced by the intravenous injection of 300 I. U. of heparin in patients with ischaemic heart disease and in a comparable control group.
developed usually about 3 hours after the fat meal and disappeared 3 hours later. There is, therefore, no reason to believe that there might be any sudden spontaneous change in the degree of lipaemia between 3 and 3½ hours after a fat meal. There was slight overlap of individual values for percentage clearing from the coronary disease group into the range of the control group, and conversely; thus the application of heparin clearing of lipaemic plasma as an adjuvant to the diagnosis of coronary artery disease is limited, perhaps by the difficulty of excluding atherosclerosis in the control group. Additional studies concerning the nature and speed of the clearing action of heparin have been described (Oliver & Boyd, 1953c) but do not come directly into the theme of this thesis.

Explanation of the difference between the coronary disease and control groups in the clearing of alimentary lipaemia by a small injection of heparin is not readily forthcoming. Exogenous heparin apparently requires some tissue component in addition to plasma in order to produce a clearing factor. Although heparin has not been detected in normal plasma, there is considerable/
siderable evidence that a heparin-like sulphated mucopolysaccharide is present in mast cells, and the physiological dissolution of chylomicra may depend upon the presence of an endogenous heparin-induced clearing factor. The postprandial lipaemia in old age and in subjects with atherosclerosis is of longer duration than in the normal, and this suggests that less endogenous clearing factor may be available in the presence of atherosclerosis. In this connection there is some histological evidence to suggest that extracellular cholesterol depositions occur at areas containing heparin-like sulphuric acid esters (Faber, 1949), and thus atherosclerotic changes might restrict the availability of an endogenous heparin-like substance and thereby reduce the concentration of circulating clearing factor.

C. CONCLUSION.

There is no doubt that the plasma cholesterol, the C/P ratio and the concentration of cholesterol on the \( \beta \)-lipoprotein fraction are all elevated in the majority of patients who have developed the clinical features of coronary atherosclerosis. These abnormalities are most marked in patients who develop symptoms under the age of 50/
50 and particularly under the age of 40. A small percentage of patients do not exhibit any abnormality in the analysis of the circulating lipids and lipoproteins and therefore such analyses cannot be used as diagnostic tests for the presence of impending ischaemic heart disease; however, they have proved to be a useful adjuvant towards the solution of an equivocal clinical diagnosis particularly in young subjects. In patients with ischaemic heart disease, in contrast to healthy men and women, a more prolonged lipaemia develops after a meal rich in fat, and the clearing of this lipaemia by heparin is less efficient and quick. Whereas this difference is obvious and significant, it is not entirely consistent and also cannot be used as a diagnostic test for the presence of impending ischaemic heart disease.

These results leave little doubt that ischaemic heart disease is frequently associated with some disturbance of the circulating lipids and lipoproteins. Moreover, a recent elaborate 4-year cooperative survey has shown conclusively that the circulating lipids and lipoproteins are abnormal before the development of any of the clinical features of coronary atherosclerosis. (Report/)
(Report of a cooperative study of the lipoproteins and atherosclerosis, 1956). This association of abnormal circulating lipids and lipoproteins with coronary atherosclerosis, together with the patchy distribution of atherosclerotic lesions, the high incidence of ischaemic heart disease in early middle age, its prevalence in males and the influence of heredity and body build, all indicate that coronary atherosclerosis is not solely an inevitable result of advancing years. It would seem reasonable to postulate that coronary atherosclerosis is an active process and is dependent, at least to some extent, on a disturbance of lipid metabolism.

Four possible explanations for this association of coronary atherosclerosis with a disturbance of lipid metabolism will now be examined:

1. It might be a chance association. This possibility can be dismissed with considerable confidence in view of the unanimity of several different investigators that such an association exists, and the statistical significance of their results.

2. It might result from a primary change within the wall of the coronary arteries, or from a/
a primary disturbance of the physiological mechanisms which normally prevent the deposition of fibrin or formation of thrombi.

Resolution of the inflammatory process, formation of fibrous and hyaline material and degenerative changes in tissues are often associated with accumulation of cholesterol esters. Whereas such changes may account for some of the cholesterol in the wall of coronary arteries, the quantity of lipid that accumulates in atherosclerotic lesions is so large as to preclude the possibility that it all originates from the simple breakdown of intimal tissue (Duff & McMillan, 1951). Furthermore, it is doubtful whether cholesterol is synthesised in any quantity, or even at all, in the arterial wall (Gould, 1951). It is likely, if any primary change takes place in the arterial wall, that the site of this change will act as a nidus for cholesterol deposition rather than a stimulus to local synthesis of cholesterol.

It is difficult to visualise how a primary disturbance of the physiological coagulation-fibrinolysis balance could result in hypercholesterolaemia, unless a change in the concentration of the various accelerators, decelerators and cofactors,
copathors, which maintain the blood in its fluid state, alter hepatic cholesterol biosynthesis at the same time. It seems improbable that deposition of fibrin or formation of a thrombus in an artery could upset the biosynthesis of cholesterol in the liver, unless fibrin is initially deposited in the hepatic rather than the coronary arteries and aorta, but there is no evidence that this is so.

3. It might contribute directly towards the development of coronary atherosclerosis. This has been and is still widely believed. Hypercholesterolaemia of some degree is nearly always essential for the production of atherosclerotic lesions in animals, and the extent and duration of the hypercholesterolaemia determines the number and the severity of atherosclerotic lesions. Moreover, there is a great deal of evidence, reviewed by Hueper (1944) and brought up to date in the section on arterial lesions (see Page 12), that plasma cholesterol passes physiologically through the vessel wall from the lumen and contributes to, or may be entirely responsible for, the cholesterol in the atherosclerotic plaque. The patchy/
patchy distribution of atherosclerotic lesions in the coronary vascular tree indicates that some parts are more prone to cholesterol deposition than others and, since the composition of the plasma which bathes the vascular lining is essentially the same in all areas, this discrete distribution of atherosclerotic lesions probably depends on local differences in the arterial wall or on local haemodynamic effects. The nature and relative importance of various local factors have not been thoroughly investigated, but variations in intimal permeability and in the metabolic activities of the intimal cellular elements in handling lipids presented to them may be important (Duff & McMillan, 1951). Certainly it is true that anoxaemia or damage to the arterial wall predisposes to cholesterol deposition and the development of atherosclerotic lesions (Hueper, 1944, 1945). Hypercholesterolaemia and instability of the cholesterol-protein attachment probably result in the accumulation of cholesterol in the intima but are certainly not the sole causes of such deposition; local and haemodynamic factors may be of equal importance.

4./
4. Abnormal metabolism of lipids and atherosclerotic lesions in the coronary arteries might both be secondary to some other alteration of physiological function. It is possible that the abnormalities in the circulating lipids and lipoproteins, the thrombotic tendency and the atherosclerotic lesions in coronary arteries all have a common denominator. This postulate will now be examined (see Part III) and a hypothesis will be developed that an alteration of normal endocrine balance might act as a common aetiological factor.
PART III
ENDOCRINE IMBALANCE AS AN AETIOLOGICAL FACTOR

A. THE INFLUENCE OF THE ENDOCRINE GLANDS AND ADMINISTERED HORMONES ON THE CIRCULATING LIPIDS AND LIPOPROTEINS.

1. The circulating lipids and lipoproteins in relation to certain physiological endocrine changes. 92
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2. The influence of hormones on the fluid state of the blood. 126
3. The influence of hormones on the arterial wall. 128

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2. The aetiology of ischaemic heart disease. 135
A. THE INFLUENCE OF THE ENDOCRINE GLANDS
AND ADMINISTERED HORMONES ON THE CIRCULATING
LIPIDS AND LIPOPROTEINS.

1. The circulating lipids and lipoproteins in
relation to certain physiological endocrine
changes.

a. Menstrual cycle.

Depression of the plasma cholesterol, the
C/P ratio and the β-lipoprotein cholesterol with
elevation of the α-lipoprotein cholesterol
occurred regularly at ovulation and during
menstruation of 24 young healthy women; and
the opposite changes in the circulating lipids and
lipoproteins developed during the luteal phase
of the cycle (see Page 58 & Figs. 8, 9 and 11).

The secretion of oestrogens also undergoes
regular cyclical variation and is generally
believed to be maximal immediately before ovula-
tion (Smith & Smith, 1936; Brown, 1955) and to
remain high throughout the luteal phase, and some
workers have observed a secondary peak just before
menstruation, (Gustavson et al, 1938). Progest-
erone secretion, as measured by urinary preg-
nanediol excretion, increases after ovulation to
reach a peak at about the 22nd day of a 28 day
cycle and thereafter gradually falls (Venning &
Brown, 1937). It seems reasonable, therefore, to
correlate the cyclical changes in the circulating
lipids and lipoproteins with the regular varia-
tions in these sex hormones; it is suggested that
the/
the decrease observed in the former at ovulation could result from the increased endogenous secretion of oestrogens and that the opposite changes observed during the luteal phase might possibly be related to the endogenous secretion of progestins. However, since there is some retention of sodium chloride and water at the time of ovulation and particularly just before menstruation (Thorn et al., 1938), the possibility cannot be entirely excluded that the observed cyclical changes may be partly the result of dilution of the plasma, even although there were no regular changes in the plasma proteins in this series of 24 women.

b. Pregnancy.

Elevation of the plasma cholesterol, the C/P ratio and the $\beta$-lipoprotein cholesterol with depression of the $\alpha$-lipoprotein cholesterol has been observed during pregnancy in 12 young healthy primigravidae (see Page 60 and Figs. 12 and 13). This hypercholesterolaemia in late pregnancy has been variously ascribed to decreased elimination of cholesterol in the bile, to increased adrenal synthesis of cholesterol, to placental toxins, to the influence of the foetus and to the metabolic requirements of lactation, but the evidence to implicate any of these/
these factors is circumstantial and unconvincing. Endocrine influences have also been suggested as a cause of the hypercholesterolaemia (Schiller, 1919; Boyd, 1934) and certainly in pregnancy there are considerable changes from the normal endocrine balance.

The behaviour of the circulating lipids and lipoproteins during pregnancy must be considered in relation to some of these endocrine changes. The concentration of oestrogens, estimated by semiquantitative measurements of urinary oestrogens, rises steadily during pregnancy until the last month when there is probably no further increase, and at term there is a sharp drop (Venning, 1946). This increase in the urinary concentration of oestrogens (which presumably reflects the concentration of circulating oestrogens) is in the region of a thousandfold, and its occurrence in association with elevation of the circulating lipids and lipoproteins is at variance with the suggestion that the endogenous secretion of oestrogens may cause depression of these values at ovulation (see Page 92) and with the observation that the administration of oestrogen/
oestrogen preparations results in depression of the circulating lipids and lipoproteins (see Page 119). It is possible that this lipid-depressant action of oestrogens is antagonised during pregnancy, or that the concentration or relative proportions of the various oestrogens are such that the depressant action is lost. The concentration of circulating progesterone, as judged by urinary pregnanediol excretion, is increased twentyfold (Venning, 1946), but administered progesterone does not cause any very striking elevation of the circulating lipids and lipoproteins (see Page 122). While androgens undoubtedly elevate these values (see Page 122) there is no evidence that androgens are secreted in excess by pregnant women, and furthermore, the 17-ketosteroid excretion is not increased (Venning, 1946).

In pregnancy there is elevation of the serum protein-bound iodine (Heinemann et al, 1948), increased radio-active iodine uptake (Pochin, 1952), and during the last 4 months elevation of the basal metabolic rate (Javert, 1940). The hypercholesterolaemia of pregnancy seems anomalous in the presence of these signs of increased thyrotrophic and/
and thyroid activity, which usually result in depression of the circulating lipids and lipoproteins (see Page 106). Adrenocortical activity, as measured by determination of the blood and urinary 17-hydroxycorticoids, is also increased during pregnancy (Venning, 1946; Gemzell, 1953), yet the administration of adrenocorticotrophic hormone and cortisone cause depression of the circulating lipids and lipoproteins (see Page 109).

The development of hypercholesterolaemia in the presence of increased oestrogenic, thyroid, and adrenocortical activity is unexpected and at present unexplained. There is evidence that the secretion of growth hormone from the hyperplastic anterior pituitary is, in common with the secretion of the other trophic hormones, increased during pregnancy (Young, 1951). Moreover, increased secretion of growth hormone may be partly responsible for the increased insulin requirement of the diabetic pregnant woman and the birth of large babies from prediabetic and diabetic mothers (Young, 1953). It is possible that more complete understanding of the interrelationship of growth hormone, glucagon and insulin may help to explain the hypercholesterolaemia of pregnancy.

c./
c. **Menopause.**

Elevation of the plasma cholesterol and C/P ratio has been observed during the first postmenopausal decade (Fig. 14 and Table VIII). This might be related to the decrease in oestrogenic activity and also to any postmenopausal decrease in thyroid or adrenocortical activity. If there is a hormonal basis for the postmenopausal rise in healthy women, it does not appear to influence hypercholesterolaemic subjects in the same way since no postmenopausal rise was observed in women with established ischaemic heart disease (Figs. 17 and 18). Explanation of the subsequent fall in the circulating lipids is not readily forthcoming; this fall has recently been confirmed by Adlersberg *et al* (1956), who observed the postmenopausal rise only between the ages of 53 and 57.

2. **Incidence of coronary disease in certain endocrine disorders.**

a. **Diabetes mellitus.**

The occurrence of coronary disease in a diabetic patient was first reported in 1864 by Seegen; subsequently it has been indicated that coronary/
coronary atherosclerosis and ischaemic heart disease are common in diabetic patients (Joslin, 1930; Blotner, 1930). Advanced and often occlusive atherosclerosis of the coronary arteries has been demonstrated at autopsy in 53% of 973 diabetic patients in contrast to 28% of 5829 non-diabetic patients of comparable age; and similarly, coronary thrombosis was observed at autopsy in 32% of 790 diabetic patients and in 16% of 5650 nondiabetic patients of comparable age (Liebow and Hillerstein, 1949). Thus coronary disease is twice as common in diabetic than in nondiabetic subjects. Provided they have the disease long enough, diabetics will almost invariably become atherosclerotic; of 484 autopsies on patients who had had diabetes for 5 or more years, only 4 were free from atherosclerosis (Warren, 1938). Diabetes also hastens the development of coronary atherosclerosis and ischaemic heart disease in youth (Joslin and Wilson, 1950) and eliminates the relative immunity of women (Clawson & Bell, 1949).

b. Myxoedema.

In 1888 a Report by the Committee of the Clinical Society of London described atheromatous changes in the arteries of only 5 out of 84 cases of myxoedema, but since then there have been frequent reports/
reports of a high incidence of coronary atherosclerosis in association with myxoedema (Black and Kampmeier, 1934; Bruger and Rosenkrantz, 1942; Means, 1948). However, the existence of this association is not universally accepted, and Andrus (1953) does not believe that there is any conclusive evidence that gross atherosclerosis is an inevitable consequence of hypothyroidism. Myxoedema has its highest incidence at ages when atherosclerosis is most common, and it is often difficult therefore to assess the influence that myxoedema may have had on the development of coronary atherosclerosis. The report of the 1888 Committee is often quoted against any correlation between myxoedema and atherosclerosis, but it should be noted that the occurrence of atherosclerosis in only 6% of the cases is much less than would be expected in autopsies of non-myxoedematous adult subjects (White et al., 1950), and the methods of assessment of atherosclerotic lesions were not very comprehensive. However, the observation of a high incidence of atherosclerosis in patients with endemic cretinism and goitre (Wegelin, 1925), and in young patients with thyroid deficiency (Fishberg, 1924; Hoelzer, 1940) offers more substantial/
substantial support for a relation between the two conditions.

The incidence of ischaemic heart disease may not be increased in untreated myxoedema (Means, 1948). Although it is probable that myxoedema favours the development of coronary atherosclerosis, the function of these diseased arteries may be quite adequate for the demands of the myocardium when metabolism is retarded. As soon as metabolism is increased by the administration of a thyroid derivative, the atherosclerotic coronary arteries become relatively inadequate and angina develops; and there is no doubt that the development of angina in treated myxoedematous patients is common (Means, 1948). Like diabetes, myxoedema may diminish the sex difference in the incidence of ischaemic heart disease; in a group of 59 cases of spontaneous myxoedema, ischaemic heart disease occurred as frequently in women under 50 as in men under 50 (Bartels & Bell, 1939). Endocrine disorders occurred in 30% of women who developed ischaemic heart disease under the age of 40 (Table XV).
Table XV. An analysis of the health of 20 women who developed ischaemic heart disease before the age of 40.

<table>
<thead>
<tr>
<th>Associated disease or disorder</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disorders:</td>
<td></td>
</tr>
<tr>
<td>Myxoedema</td>
<td>2</td>
</tr>
<tr>
<td>Menopause aged 32</td>
<td>1</td>
</tr>
<tr>
<td>Ovariectomy, aged 22</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Cushing’s disease</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
</tr>
<tr>
<td>During pregnancy or puerperium</td>
<td>4</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1</td>
</tr>
<tr>
<td>No associated disease</td>
<td>4</td>
</tr>
</tbody>
</table>

c. Hyperadrenocorticism (Cushing's Disease). Atherosclerosis was observed in 3 out of 9 autopsied cases originally described by Cushing (1932), and extensive calcification was apparent radiologically in the aorta of his first case; all 4 were under the age of 28 years. Generalised vascular sclerosis has been reported in 6 patients who died from Cushing's disease or hyperadrenocorticism, and cholesterol deposits have been observed in the endothelium of small arteries (Heinbecker, 1944); 5 of these 6 patients died under the age of 33 years. Subsequently, the statement that atherosclerosis, especially of the coronary/
coronary arteries, occurs with increased frequency in Cushing's disease has often been made without detailed evidence to support this contention (Williams, 1951; Wakerlin, 1952; Katz & Stamler, 1953); however, Thompson and Eisenhardt (1943) reported 98 cases, of whom 63 had an autopsy, without mention of atherosclerosis. Cushing's disease is associated very frequently with hypertension and diabetes and often with depression of thyroid function, and any premature development or increase in the incidence of atherosclerosis may well be related to these other influences. The suggestion that atherosclerosis develops earlier and to a greater degree in Cushing's disease is not well documented or controlled, and the evidence that it results from hyperadrenocorticism is largely circumstantial.

d. Castration.

Examination of the hearts of 49 women, in whom bilateral ovariectomy was performed between the ages of 2 and 42 years, revealed more severe coronary atherosclerosis, decade for decade, than the average degree of coronary atherosclerosis of a control group (Wuest et al, 1953); yet only 3/
3 of these 49 patients were found to have had clinical manifestations of coronary disease. No other comparable investigation has yet been reported and no studies of the hearts of male castrates have been recorded.

3. The circulating lipids and lipoproteins in certain endocrine disorders.

a. Diabetes mellitus.

There is little doubt that the frequency and severity of atherosclerosis in diabetes can be correlated with the duration of uncontrolled glycosuria and hyperglycaemia and with the concomitant hyperlipaemia and hypercholesterolaemia (Joslin et al, 1946). Hyperlipaemia is more marked than hypercholesterolaemia (Hirsch et al, 1953), yet of a series of 273 diabetic patients 50% exhibited elevated circulating lipids while 92% of those with severe atherosclerosis showed hyperlipaemia (Pomeranze and Kunkel, 1950). Hypercholesterolaemia was often observed in young diabetics (Rabinowitch, 1935). Ultracentrifuge studies in diabetics have shown abnormally high concentrations of the particular cholesterol-containing lipoproteins (S_f 12-20 class) which are associated with atherosclerosis (Gofman et al, 1950). The \( \beta \)-lipoprotein cholesterol is higher in diabetics with atherosclerosis/
atherosclerosis than in diabetics without atherosclerosis, and higher in the latter group than in nondiabetics (Baker et al, 1955). Nearly all the diabetic patients seen in the Department of Cardiology had co-existent vascular disease, and no comprehensive analysis has been made in diabetics without vascular disease; however, Table XVI demonstrates the degree of abnormality of the circulating lipids and lipoproteins in a man of 19, in whom diabetes presented by the development of diffuse eruptive cutaneous xanthoma.

Table XVI. The circulating lipids in a 19 year old man with xanthoma diabeticorum. Insulin was started on 1.8.55.

<table>
<thead>
<tr>
<th>Date</th>
<th>Plasma cholesterol mg%</th>
<th>C/P Ratio</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8.1955</td>
<td>1230</td>
<td>1.71</td>
<td>Diffuse xanthomatous eruption and very lipaemic.</td>
</tr>
<tr>
<td>3.8.1955</td>
<td>720</td>
<td>1.21</td>
<td>Lipaemic</td>
</tr>
<tr>
<td>6.8.1955</td>
<td>172</td>
<td>0.78</td>
<td>Clear plasma</td>
</tr>
</tbody>
</table>

Diabetes is, therefore, associated with abnormal circulating lipids and lipoproteins and a parallel relationship exists between hyperlipaemia and hyperglycaemia (Hirsch et al, 1953). These/
105.

These abnormalities of the circulating lipids and lipoproteins are probably a direct consequence of insulin lack, but they may also depend partly on the degree of renal damage associated with intercapillary glomerulo-sclerosis; tubular insufficiency and proteinuria in nephrosis is associated with both hyperlipaemia and hypercholesterolaemia (Peters & Man, 1943c).

b. Myxoedema.

It is well known that myxoedema is associated with hypercholesterolaemia (Mason et al, 1930; Hurxthal, 1934; Gildea et al, 1939). This increase in circulating cholesterol is not due solely to lowered metabolism, since dinitro-β-cresol will restore metabolism to normal without reducing the hypercholesterolaemia associated with hypothyroidism (Dodds & Robertson, 1933) and reduction in metabolism in euthyroid subjects is not accompanied by hypercholesterolaemia (Mason et al, 1930). In myxoedema the concentration of cholesterol on the β-lipoprotein fraction is elevated (Malmros & Swahn, 1953), and ultracentrifuge studies have indicated that the concentration of the potentially atherogenic (Sf 12–20) class of lipoproteins is also increased (Gofman et al, 1950).

c./
c. **Thyrotoxicosis.**

It is well established that the circulating cholesterol is low when there is hyperfunction of the thyroid (Epstein & Lande, 1922; Mason et al, 1930; Peters & Man, 1943). The plasma cholesterol is generally lowest in patients with very marked hyperthyroidism, but there is no absolute direct correlation with the height of the basal metabolic rate.

d. **Hyperadrenocorticism (Cushing's Disease).**

Analyses of the circulating lipids in hyperadrenocorticism have not been reported frequently. The blood cholesterol was reported in 5 of Cushing's cases and was elevated in one (Cushing, 1932); there appears to be no consistent abnormality, although there is occasionally hypercholesterolaemia (Heinbecker, 1944; Heinbecker & Pfeiffenberger, 1950) but hypercholesterolaemia has also been reported in Addison's disease (Medvei, 1935). Peters and Van Slyke (1946) believe that any hypercholesterolaemia, which may occur in association with hyperadrenocorticism, can be explained by accompanying diabetes and renal damage. Thus, there is no convincing evidence that Cushing's disease is associated with hypercholesterolaemia or with an increased incidence of atherosclerosis and ischaemic heart disease (Page 101).
e. Castration.

No study of the circulating lipids and lipoproteins has yet been reported after gonadectomy, but in 2 out of 3 patients, in whom bilateral ovariectomy had been carried out, there was elevation of the circulating lipids and lipoproteins (Table XVII); angina occurred in 1 woman at the age of 38 and a myocardial infarct developed in another at the age of 49. In the third patient, there was auricular fibrillation and mild thyrotoxicosis, which might account for the normal circulating lipid levels.

Table XVII. The circulating lipids and lipoproteins in 3 castrated women.

<table>
<thead>
<tr>
<th></th>
<th>Plasma cholesterol mg%</th>
<th>C/P ratio</th>
<th>α:β lipoprotein ratio</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aged 38, Ovariectomy, aged 22</td>
<td>288</td>
<td>1.96</td>
<td>9:91</td>
<td>Angina</td>
</tr>
<tr>
<td>2. Aged 49, Ovariectomy, aged 27</td>
<td>577</td>
<td>1.56</td>
<td>4:96</td>
<td>Myocardial infarct</td>
</tr>
<tr>
<td>3. Aged 52, Ovariectomy, aged 31</td>
<td>201</td>
<td>0.87</td>
<td>-</td>
<td>Auricular fibrillation and mild thyrotoxicosis</td>
</tr>
</tbody>
</table>
4. The influence of hormones on the circulating lipids and lipoproteins.

The effect of extraneous influences on the circulating cholesterol, such as a dietary constraint or the administration of hormones, may be delayed for several days. The "half-life" of the circulating cholesterol is 8 days (London and Rittenberg, 1950), and thus any change in the circulating cholesterol or the concentration of cholesterol on the $\beta$-lipoprotein fraction resulting from an alteration in the rate of biosynthesis or degradation will be delayed. However, when there is a redistribution of cholesterol between the cells and extracellular fluid (such as may occur after the administration of certain thyroxine analogues), the effect on the circulating cholesterol could be apparent within a day or two.

In general the subjects of these investigations were either healthy men, or hypercholesterolaemic men with ischaemic heart disease and electrocardiographic evidence of a myocardial infarct. It was not considered justifiable to administer hormones with a pronounced metabolic effect, such as ACTH, cortisone and the sex hormones, to healthy subjects.

a./
a. Pituitary hormones.

i. Adrenocorticotropic hormone.

The daily intramuscular administration of 50 mg. adrenocorticotropic hormone (ACTH) for 8 days resulted in significant depression of the plasma cholesterol, the C/P ratio and the \( \beta \)-lipoprotein cholesterol with elevation of the \( \alpha \)-lipoprotein cholesterol in 6 hypercholesterolaemic men with proven coronary disease (Table XVIII). The daily administration of 100 mgm. of ACTH for 5 days resulted in similar changes in the circulating lipids and lipoproteins in a further 6 hypercholesterolaemic men with proven coronary disease (Fig. 21 and Table XVIII) (Oliver & Boyd, 1955c, 1956b). These results confirm the experiences of Conn et al., (1950) in 3 normal men but appear to contradict the observations of Adlersberg et al., (1950, 1951); this apparent discrepancy will be considered later (see section concerning cortisone on page 111).

ii. Thyroid stimulating hormone.

The daily intramuscular administration of 10 units of thyroid stimulating hormone (TSH) for 4 days did not cause any significant change in the circulating lipids and lipoproteins in 3 subjects with primary myxoedema (Table XVIII) (Oliver and Boyd, 1956b). The/
Table XVIII. The effect of pituitary hormones on the circulating lipids and lipoproteins in hypercholesterolaemic men.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Number of subjects</th>
<th>Plasma cholesterol mg%</th>
<th>C/P ratio</th>
<th>β-lipoprotein cholesterol</th>
<th>α-lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocorticotrophin:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(intramuscularly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg. daily for 8 days</td>
<td>6</td>
<td>-15%</td>
<td>-5%</td>
<td>-22%</td>
<td>+16%</td>
</tr>
<tr>
<td>100 mg. daily for 5 days</td>
<td>6</td>
<td>-16%</td>
<td>-16%</td>
<td>-30%</td>
<td>+57%</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(intramuscularly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 units daily for 4 days</td>
<td>3</td>
<td>No significant change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>to hypothyroid men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 units daily for 4 days</td>
<td>3</td>
<td>-28%</td>
<td>-16%</td>
<td>-21%</td>
<td>+24%</td>
</tr>
<tr>
<td>to euthyroid men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth hormone:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(intravenously)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg. over 30 minutes</td>
<td>3</td>
<td>No significant change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>to healthy men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig. 21. The changes in the circulating lipids and lipoproteins during the intramuscular administration of 100 mg of ACTH daily to 6 hypercholesterolaemic men with ischaemic heart disease.
The intramuscular administration of the same dose of TSH for 4 days to 3 hypercholesterolaemic men with coronary disease resulted in significant depression of the circulating lipids and lipoproteins (Table XVIII). These results suggest that TSH has no direct action on the circulating lipids and lipoproteins, and that any effect in euthyroid subjects is mediated through stimulation of functioning thyroid tissue.

iii. Growth hormone.

The intravenous infusion over a period of 30 minutes of 180 ml. of normal saline containing 200 mg. of a porcine growth hormone (STH) preparation did not result in any immediate or delayed change in the circulating lipids and lipoproteins in 3 healthy men (Table XVIII). This same growth hormone preparation was known to be effective in rats in stimulating hepatic cholesterol biosynthesis after inhibition by hypophysectomy. It is unlikely, therefore, that the preparation was metabolically inert, although it is possible that the dose was too small to produce any effect on the circulating lipids and lipoproteins; this may be so, but it has been shown that a similar dose resulted in a fall in blood/
blood aminoacid nitrogen and hyperglycaemia (Carballeira et al, 1952). It is possible that prolonged intramuscular administration of a crystalline growth hormone preparation (not widely available) or of a human growth hormone preparation might influence the circulating lipids and lipoproteins, although in general the metabolic activity of growth hormone preparations is disappointing at present.

iv. Gonadotrophic hormones

Preparations of gonadotrophic hormones, whether predominantly follicular-stimulating or luteinising, have not been administered in man with the object of assessing their influence on the circulating lipids and lipoproteins. Animal assays have indicated that these preparations do not have either a purely follicular-stimulating or a purely luteinising action, and thus it was considered that study of the influence of the individual sex hormones on the circulating lipids and lipoproteins would be of greater value.

b. Adrenal cortical hormones

i. Cortisone

The daily oral administration of 100 mg.
of cortisone acetate for 10 days resulted in significant depression of the plasma cholesterol, the C/P ratio and the β-lipoprotein cholesterol with elevation of the α-lipoprotein cholesterol in 6 hypercholesterolaemic men with proven coronary disease (Fig. 22 and Table XIX). The daily administration of 150 mg. and of 200 mg. of cortisone acetate each for 10 days resulted in similar changes in the circulating lipids and lipoproteins in two further groups of 6 hypercholesterolaemic men with proven coronary disease (Table XIX)(Oliver and Boyd, 1955c, 1956b).

The influence of cortisone acetate on the circulating lipids and lipoproteins is, therefore, similar to that of ACTH. These results in hypercholesterolaemic subjects, all of whom were at work and reasonably healthy, do not necessarily contradict those of Adlersberg et al. (1950, 1951), who showed that ACTH and cortisone raised the serum cholesterol in patients who were severely ill with diffuse lupus erythematosus, polyarteritis nodosa, dematomyositis and other collagen diseases. In their cases the symptomatic improvement, the reduction of fever, and the/
The changes in the circulating lipids and lipoproteins during the oral administration of 100 mg of cortisone acetate daily to 6 hypercholesterolaemic men with ischaemic heart disease.
Table XIX. The effect of cortisone acetate and desoxycorticosterone acetate on the circulating lipids and lipoproteins in hypercholesterolaemic men with coronary disease.

<table>
<thead>
<tr>
<th></th>
<th>Number of subjects</th>
<th>Plasma cholesterol mg%</th>
<th>C/P ratio</th>
<th>β-lipoprotein cholesterol</th>
<th>α-lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortisone acetate:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(orally)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg daily for 10 days</td>
<td>6</td>
<td>-12%</td>
<td>-9%</td>
<td>-16%</td>
<td>+17%</td>
</tr>
<tr>
<td>150 mg daily for 10 days</td>
<td>6</td>
<td>-15%</td>
<td>-11%</td>
<td>-17%</td>
<td>+11%</td>
</tr>
<tr>
<td>200 mg daily for 10 days</td>
<td>6</td>
<td>-13%</td>
<td>-2%</td>
<td>-28%</td>
<td>+47%</td>
</tr>
<tr>
<td><strong>Desoxycorticosterone acetate:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(intramuscularly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg daily for 5 days</td>
<td>6</td>
<td>-6%</td>
<td>-4%</td>
<td>-10%</td>
<td>+48%</td>
</tr>
</tbody>
</table>
the return of appetite probably contributed to the rise in circulating cholesterol; moreover, in the few of their patients who were hypercholesterolaemic and who had some disease other than a collagen disorder, the plasma cholesterol was not significantly raised by ACTH and cortisone. Mann and White (1953) considered that any elevation of the plasma cholesterol produced by ACTH and cortisone could be due to relief of the acutely stressful phase of the disease in these very ill patients, thus permitting the low cholesterol levels to return to normal; certainly in Adlersberg's cases the initial levels of circulating cholesterol were unusually low in contrast to the values obtained in healthy American adults.

The response of the circulating lipids and lipoproteins to ACTH and cortisone in the 30 men referred to in Tables XVIII and XIX was remarkably uniform, and it is believed that, although these men were initially hypercholesterolaemic, depression of these values may be the true response to ACTH and cortisone.

ii. Desoxycorticosterone acetate.
115.

ii. Desoxycorticosterone acetate. Although desoxycorticosterone acetate (DOCA) is probably not a natural secretion of the adrenal cortex, it has been included in this section on the assumption that its effect on the circulating lipids and lipoproteins will represent the effect of naturally-occurring mineralocorticoids. The daily intramuscular administration of 5 mg. of desoxycorticosterone acetate for 5 days resulted in slight depression of the plasma cholesterol, the C/P ratio and the \( \beta \)-lipoprotein cholesterol with increase in the \( \alpha \)-lipoprotein cholesterol in 6 hypercholesterolaemic men with proven coronary disease (Table XIX); the packed cell volume was reduced by 6%.

c. Thyroid hormones.

It has been known for many years that thyroid extract lowers the plasma cholesterol and phospholipids in hypothyroid and in euthyroid subjects, and at the same time increases their metabolic requirements (Lévy & Lévy, 1931; Turner & Steiner, 1939; Gildea et al, 1939); and more recently it has been shown that thyroxine also reduces the \( \beta \)-lipoproteins (Maimros & Swahn, 1953) and/
and lowers the concentration of the "atherogenic group" of low density lipoproteins ($S_f 12-20$) as determined by the ultracentrifuge (Strisower et al, 1954). The principle hormones secreted by the thyroid are thyroxine and triiodothyronine, which is derived from thyroxine by deiodination and probably has similar physiological actions.

i. $l$-thyroxine sodium.

**Hypothyroid subjects.** The daily oral administration of $300 \mu g$ of $l$-thyroxine sodium for 8 weeks resulted in significant depression of the plasma cholesterol, $C/P$ ratio and the $\beta$-lipoprotein cholesterol with elevation of $\alpha$-lipoprotein cholesterol in 6 patients with classical myxoedema (Fig. 23 and Table XX). The mean weight loss was 7 lbs, and the basal metabolic rate was increased by 17%.

**Euthyroid subjects.** The daily oral administration of $600 \mu g$ of $l$-thyroxine sodium for 2 weeks resulted in similar changes in a further 6 euthyroid hypercholesterolaemic men with proven coronary disease (Fig. 24 and Table XXI), except that the concentration of cholesterol on the $\alpha$-lipoprotein fraction also fell. The mean weight loss after 3 weeks was 4 lbs. and the basal metabolic rate increased by 13%.

ii./
Fig. 23. The changes in the circulating lipids and lipoproteins, and in the basal metabolic rate and weight, during the oral administration of 300 µg. of l-thyroxine sodium daily to 6 patients with myxoedema.
Table XX. The effect of thyroxine and some analogues on the circulating lipids and lipoproteins in hypercholesterolaemic hypothyroid patients.

<table>
<thead>
<tr>
<th></th>
<th>Number of subjects</th>
<th>Plasma cholesterol mg%</th>
<th>C/P ratio</th>
<th>β-lipoprotein cholesterol</th>
<th>α-lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>l-thyroxine sodium:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 μg. daily for 8 weeks</td>
<td>6</td>
<td>-40%</td>
<td>-6%</td>
<td>-29%</td>
<td>+42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>l-triiodothyronine:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 μg. daily for 10 days</td>
<td>2</td>
<td>-22%</td>
<td>-7%</td>
<td>-18%</td>
<td>+31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triiodothyroacetic acid:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 mg. daily for 17 days</td>
<td>1</td>
<td>-31%</td>
<td>-10%</td>
<td>-40%</td>
<td>+38%</td>
</tr>
<tr>
<td>5 mg. daily for 6 days</td>
<td>2</td>
<td>-37%</td>
<td>-23%</td>
<td>-26%</td>
<td>+35%</td>
</tr>
</tbody>
</table>
The changes in the circulating lipids and lipoproteins and in weight during the oral administration of 600 μg. of \( l \)-thyroxine sodium to 6 euthyroid hypercholesterolaemic men with ischaemic heart disease.

![Graph showing changes in plasma cholesterol, % change in lipoprotein cholesterol, C/P ratio, weight, and dose of \( l \)-thyroxine sodium over 12 weeks.]
Table XXI. The effect of thyroxine and some analogues on the circulating lipids and lipoproteins in hypercholesterolaemic euthyroid men with coronary disease.

<table>
<thead>
<tr>
<th>L-thyroxine sodium:</th>
<th>Number of subjects</th>
<th>Plasma cholesterol mg%</th>
<th>C/P ratio</th>
<th>β-lipoprotein cholesterol</th>
<th>α-lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 μg. daily for 2 weeks</td>
<td>6</td>
<td>-27%</td>
<td>-17%</td>
<td>-29%</td>
<td>-20%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>L-triiodothyronine:</th>
<th>Number of subjects</th>
<th>Plasma cholesterol mg%</th>
<th>C/P ratio</th>
<th>β-lipoprotein cholesterol</th>
<th>α-lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>±40-60 μg. daily over 8 weeks</td>
<td>3</td>
<td>-16%</td>
<td>-11%</td>
<td>-27%</td>
<td>+4.2%</td>
</tr>
<tr>
<td>40-100 μg. daily over 7 weeks</td>
<td>3</td>
<td>-34%</td>
<td>-17%</td>
<td>-36%</td>
<td>-12%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Triiodothyroacetic acid:</th>
<th>Number of subjects</th>
<th>Plasma cholesterol mg%</th>
<th>C/P ratio</th>
<th>β-lipoprotein cholesterol</th>
<th>α-lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>±0.5-4 mg. daily over 12 weeks</td>
<td>6</td>
<td>-21%</td>
<td>-12%</td>
<td>-26%</td>
<td>+4.5%</td>
</tr>
</tbody>
</table>

† No elevation of basal metabolic rate.
ii. \( l \)-triiodothyronine.

**Hypothyroid subjects.** The daily oral administration of 30 \( \mu g \) of \( l \)-triiodothyronine for 10 days resulted in depression of the plasma cholesterol, the \( C/P \) ratio and the \( \beta \)-lipoprotein cholesterol with elevation of the \( \alpha \)-lipoprotein cholesterol in 2 patients with classical myxoedema. The mean weight loss was 6 lbs. and the basal metabolic rate increased by 15\% (Table XX).

**Euthyroid subjects.** The daily oral administration of 40 \( \mu g \) of \( l \)-triiodothyronine for 5 weeks and then 60 \( \mu g \) for 2 weeks to 3 euthyroid hypercholesterolaemic men with proven coronary disease resulted in significant depression of the plasma cholesterol, the \( C/P \) ratio, and the \( \beta \)-lipoprotein cholesterol with elevation of the \( \alpha \)-lipoprotein cholesterol (Table XXI). There was no change in weight or in the basal metabolic rate.

The daily oral administration of a larger dose (40 \( \mu g \) for 2 weeks and then 100 \( \mu g \) for 4 weeks) of \( l \)-triiodothyronine resulted in similar changes in the circulating lipids and lipoproteins, except that the concentration of cholesterol/
cholesterol on the $\alpha$-lipoprotein fraction also fell, in a further 3 euthyroid hypercholesterolaemic men with proven coronary disease (Fig. 25 and Table XXI). The mean weight loss was 6 lbs. and the basal metabolic rate increased by 11%.

iii. Triiodothyroacetic acid.

Triiodothyronine can undergo oxidative deamination to triiodothyropyruric acid with subsequent oxidative decarboxylation of the latter compound to triiodothyroacetic acid (triac); this acetic acid analogue of triiodothyronine was first synthesised by Pitt-Rivers (1953).

Hypothyroid subjects. The daily oral administration of 0.5 mg. of triac for 21 days resulted in significant depression of the plasma cholesterol, the C/P ratio and $\beta$-lipoprotein cholesterol with elevation of the plasma cholesterol in a 69 year old woman with classical myxoedema (Fig. 26 and Table XX). There was no weight loss and no increase in the basal metabolic rate. The daily oral administration of a larger dose (4 mg. for 6 days) of triac resulted in similar changes in the circulating lipids and lipoproteins in 2 patients with classical myxoedema (Fig. 27 and Table XX). Within 24 hours there was/
Fig. 25. The changes in the circulating lipids and lipoproteins, and in the basal metabolic rate and weight, during the oral administration of 40 and 100 μg. of \( \ell \)-triiodothyronine daily to 3 euthyroid hypercholesterolaemic men with ischaemic heart disease.
The changes in the circulating lipids and lipoproteins, and in the basal metabolic rate and weight, during the oral administration of 500 µg. of triiodothyroacetic acid daily to a 69 year old woman with myxoedema.
Fig. 27. The changes in the circulating lipids and lipoproteins, and in the basal metabolic rate and weight, during the oral administration of 4 mg of triiodothyronic acid daily to 2 patients with myxoedema.
was improvement of the clinical signs of myxoedema, weight loss and an increase in the basal metabolic rate.

**Euthyroid subjects.** The daily oral administration of increasing doses (from 0.5 mg. to 4 mg.) of triac over a period of 95 days resulted eventually in depression of the plasma cholesterol, the C/P ratio and the $\beta$-lipoprotein cholesterol with elevation of the $\alpha$-lipoprotein cholesterol in 6 euthyroid hypercholesterolaemic men with proven coronary disease; there was no significant effect until 3 mg. of triac were administered daily (Fig. 28 and Table XXI). There was no weight loss, and the mean basal metabolic rate was not significantly altered although it was elevated in two of the men by 13% and 20% respectively. The action of some of these thyroid hormones has been described recently (Oliver & Boyd, 1957, Boyd and Oliver, 1957), and their potential therapeutic application will be considered later (see Page 153).

d. **Sex hormones**

i. **Oestrogens**

The suggestion that depression of the circulating/
Fig. 28. The changes in the circulating lipids and lipoproteins, and in the basal metabolic rate and weight, during the oral administration of increasing doses of triiodothyroacetic acid daily to euthyroid hypercholesterolaemic men with ischaemic heart disease.
circulating cholesterol, the C/P ratio and \( \beta \)-lipoprotein cholesterol at ovulation (see Page 92) might be due to endogenous secretion of oestrogens indicated that the influence of administered oestrogens on the circulating lipids and lipoproteins required assessment.

(1) Ethinyl oestradiol.

**Pilot study.** As the circulating lipids had not previously been studied after the administration of oestrogens, a small pilot study was necessary in order to determine the minimal dose required to alter these values. After a control period of 7 weeks, ethinyl oestradiol was administered orally to 3 hypercholesterolaemic men with proven coronary disease and the dose was gradually increased over the next 10 weeks from 0.02 mg. to 0.4 mg. daily. The mean plasma cholesterol remained constant up to a dose of 0.2 mg. of ethinyl oestradiol, but thereafter decreased significantly (Fig. 29). This preliminary study suggested that the effective oral dose of ethinyl oestradiol would not be less than 0.2 mg. daily. *(Oliver and Boyd, 1954).*

**Graduated study.** The daily oral administration of increasing doses from 0.2 mg. to/
Fig. 29. The changes in the circulating lipids during a pilot study of the oral administration of ethinyl oestradiol to 3 hypercholesterolaemic men with ischaemic heart disease.
to 1 mg. of ethinyl oestradiol over a period of 12 weeks to 15 hypercholesterolaemic men with proven coronary disease resulted in significant depression of the plasma cholesterol and C/P ratio (Fig. 30 and Table XXII). Ethinyl oestradiol and other oestrogens decrease the \( \beta \)-lipoprotein cholesterol and increase the \( \alpha \)-lipoprotein cholesterol (Fig. 31).

**Large dose study.** The daily oral administration of 1 mg. of ethinyl oestradiol for 6 weeks to 30 hypercholesterolaemic men with proven coronary disease resulted in similar changes in the circulating lipids and lipoproteins (Fig. 32 and Table XXII).

Further experience concerning the administration of ethinyl oestradiol to hypercholesterolaemic men with coronary disease will be considered in the section concerning therapeutic implications (see Page 158).

(2) Hexoestrol & Stilboestrol.

The daily oral administration of 60 mg. of hexoestrol for 14 days to 6 hypercholesterolaemic men with proven coronary disease also resulted in significant depression of the plasma cholesterol/
The changes in the circulating lipids during the oral administration of increasing doses of ethinyl oestradiol to 15 hypercholesterolaemic men with ischaemic heart disease.
Table XXII. The effect of oestrogens on the circulating lipids and lipoproteins in hypercholesterolaemic men with coronary disease.

<table>
<thead>
<tr>
<th></th>
<th>Number of subjects</th>
<th>Plasma cholesterol mg%</th>
<th>C/P ratio</th>
<th>β-lipoprotein cholesterol</th>
<th>α-lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethinyl oestradiol:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing dose to 1 mg.</td>
<td>15</td>
<td>-23%</td>
<td>-33%</td>
<td>-30%</td>
<td>+61%</td>
</tr>
<tr>
<td>1 mg. daily for 6 weeks.</td>
<td>30</td>
<td>-16%</td>
<td>-23%</td>
<td>-20%</td>
<td>+29%</td>
</tr>
<tr>
<td>Hexoestrol:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 mg. daily for 2 weeks.</td>
<td>6</td>
<td>-9%</td>
<td>-16%</td>
<td>-13%</td>
<td>+30%</td>
</tr>
<tr>
<td>Stilboestrol:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg. daily for 4 weeks.</td>
<td>3</td>
<td>-11%</td>
<td>-10%</td>
<td>-12%</td>
<td>+21%</td>
</tr>
<tr>
<td>Oestradiol:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mg. daily for 2 weeks.</td>
<td>3</td>
<td>-8%</td>
<td>-8%</td>
<td>-19%</td>
<td>+15%</td>
</tr>
<tr>
<td>24 mg. daily for 2 weeks.</td>
<td>3</td>
<td>-12%</td>
<td>-8%</td>
<td>-16%</td>
<td>+19%</td>
</tr>
<tr>
<td>Oestrone:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 mg. daily for 2 weeks.</td>
<td>3</td>
<td>-3%</td>
<td>-3%</td>
<td>-2%</td>
<td>+14%</td>
</tr>
<tr>
<td>50 mg. daily for 2 weeks.</td>
<td>3</td>
<td>-9%</td>
<td>0</td>
<td>-6%</td>
<td>+20%</td>
</tr>
<tr>
<td>Oestriol (intramuscularly):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg. daily for 1 week.</td>
<td>2</td>
<td>-25%</td>
<td>-6%</td>
<td>-30%</td>
<td>+71%</td>
</tr>
</tbody>
</table>
Fig. 31. The changes in the circulating lipoprotein cholesterol during the oral administration of ethinyl oestradiol to hypercholesterolaemic men with ischaemic heart disease.

(The serum is applied to the filter paper at the point represented by the vertical line and is induced to migrate towards the anode represented by the +).

Cholesterol attached to the β and α lipoproteins before and during oestrogen therapy in hypercholesterolaemic males with coronary sclerosis as determined by filter paper electrophoresis.
Fig. 32. The changes in the circulating lipids during the oral administration of 1 mg of ethinyl oestradiol daily to 30 hypercholesterolaemic men with ischaemic heart disease.
cholesterol, C/P ratio and $\beta$-lipoprotein cholesterol with elevation of the $\alpha$-lipoprotein cholesterol (Table XXII); the administration of 5 mg. of stilboestrol for 4 weeks to 3 hypercholesterolaemic men with coronary disease produced comparable results (Table XXII).

(3) Naturally occurring oestrogens.

The administration of oestradiol, oestrone or oestriol to 15 hypercholesterolaemic men with coronary disease resulted in similar depression of the plasma cholesterol, the C/P ratio and the $\beta$-lipoprotein cholesterol with elevation of the $\alpha$-lipoprotein cholesterol (see Table XXII).

ii. Progesterone

The daily intramuscular administration of 100 mg. of progesterone for 5 days to 6 hypercholesterolaemic men with proven coronary disease resulted in slight but probably insignificant elevation of the circulating lipids and lipoproteins (Table XXIII).

iii. Androgen

The daily sublingual administration of 50 mg. of methyl testosterone for 10 days to 6 hypercholesterolaemic men with coronary disease resulted in/
Table XXIII. The effect of progesterone and methyl testosterone on the circulating lipids and lipoproteins in hypercholesterolaemic men with coronary disease.

<table>
<thead>
<tr>
<th></th>
<th>Number of subjects</th>
<th>Plasma cholesterol mg%</th>
<th>C/P ratio</th>
<th>β-lipoprotein cholesterol</th>
<th>α-lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone (intramuscularly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg. daily for 5 days</td>
<td>6</td>
<td>+5%</td>
<td>+8%</td>
<td>+3%</td>
<td>+27%</td>
</tr>
<tr>
<td>Methyl testosterone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg. daily for 10 days</td>
<td>6</td>
<td>+30%</td>
<td>-4%</td>
<td>+11%</td>
<td>-55%</td>
</tr>
<tr>
<td>20 mg. daily for 4 weeks after ethinyl oestradiol administration</td>
<td>12</td>
<td>+50%</td>
<td>+43%</td>
<td>-26%</td>
<td></td>
</tr>
</tbody>
</table>
in elevation of the plasma cholesterol and \( \beta \)-lipoprotein cholesterol with depression of the \( \alpha \)-lipoprotein cholesterol (Fig. 33 and Table XXIII). This action of methyl testosterone was even more pronounced when administered immediately after a course of ethinyl oestradiol (Fig. 43 and Table XXIII).

The influence of some of these sex hormones on the circulating lipids and lipoproteins in men with ischaemic heart disease has been reported recently (Oliver and Boyd, 1956a, 1956b).

e. Pancreatic hormones.

i. Glucagon.

The intravenous infusion of 2 mg. of glucagon ("hyperglycaemic factor of the pancreas") over a period of 30 minutes to 3 healthy men resulted in immediate elevation of the blood glucose and 6 days later slight elevation of the plasma cholesterol and \( \beta \)-lipoprotein cholesterol with depression of the \( \alpha \)-lipoprotein cholesterol (Fig. 34 and Table XXIV) (Oliver and Boyd, 1956b).

ii. Insulin.

The daily subcutaneous administration of 50 units of insulin for a period of 5 weeks to 6 men, who were suffering from depressive states (in Jordanburn Nerve Hospital), but were otherwise healthy, did not result in any significant change in the circulating lipids and lipoproteins. (Table XXIII)
Fig. 33. The changes in the circulating lipids and lipoproteins during the oral administration of 50 mg of methyl testosterone daily to 6 hypercholesterolaemic men with ischaemic heart disease.
The changes in the plasma cholesterol and the blood glucose following the intravenous infusion of 2 mg. of glucagon in 180 ml. of isotonic saline to 3 healthy men.
Table XXIV. The effect of glucagon and insulin on the circulating lipids and lipoproteins in healthy and diabetic men.

<table>
<thead>
<tr>
<th></th>
<th>Number of subjects</th>
<th>Plasma cholesterol mg%</th>
<th>C/P ratio</th>
<th>β-lipoprotein cholesterol</th>
<th>α-lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucagon (intravenously):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect of 2 mg. 6 days later</td>
<td>3</td>
<td>+10%</td>
<td>+2%</td>
<td>+13%</td>
<td>-10%</td>
</tr>
<tr>
<td><strong>Insulin (subcutaneously):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 units daily for 4 weeks</td>
<td>3</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>32 units daily for 6 weeks (average dose)</td>
<td>6</td>
<td>-48%</td>
<td>-12%</td>
<td>-26%</td>
<td>+52%</td>
</tr>
</tbody>
</table>
(Table XXIII), although the induced hypoglycaemia stimulated the patients to eat and they increased in weight by an average of 10 lbs. The daily subcutaneous administration of insulin to 6 hypercholesterolaemic diabetic patients resulted in significant depression of the plasma cholesterol, the C/P ratio and $\beta$-lipoprotein cholesterol with an increase in $\alpha$-lipoprotein cholesterol; these changes occurred in parallel with the fall in blood sugar (Table XXIV).

B. THE INFLUENCE OF HORMONES ON THE DEVELOPMENT OF CORONARY ATHEROSCLEROSIS AND ISCHAEMIC HEART DISEASE.

In the belief that abnormal cholesterol metabolism, a thrombotic tendency and local haemodynamic disturbances in the arterial wall all favour the development of coronary atherosclerosis and ischaemic heart disease, the influence of hormones on cholesterol metabolism, the fluid state of the blood and the arterial wall will now be considered.

1. The influence of hormones on cholesterol metabolism.

It has already been indicated that the sex/
sex hormones probably exert a physiological influence on the circulating lipids and lipoproteins. It has also been emphasised that in patients with certain endocrine disorders, such as diabetes and myxoedema, there is an unusually high incidence of coronary atherosclerosis and clinical coronary disease. Furthermore, in patients with these same endocrine disorders, yet without any features of coronary disease, analysis of the circulating lipids and lipoproteins frequently reveals the abnormal patterns associated with overt ischaemic heart disease. The administration of certain hormones has resulted in alterations in the circulating lipids and lipoproteins, and these hormonal influences are summarised in Fig. 35. Administration of adrenal, thyroid and oestrogen preparations reduces the circulating cholesterol if it is high, and administration of androgens, and possibly also of glucagon and progesterone, raises the circulating cholesterol above normal levels. There is, then, little doubt that the endocrine glands and hormones can influence cholesterol metabolism.
Fig. 35. Summary of the actions of administered hormones on the circulating cholesterol.

HYPERCHOLESTEROLAEMIA

| Adrenal + | Androgens + |
| Thyroid + | ? Glucagon+ |
| Oestrogens + | ? Progesterone+ |

NORMOCHOLESTEROLAEMIA
2. The influence of hormones on the fluid state of the blood.

a. Fibrinogenesis.

The coagulation system may reasonably be regarded as consisting of two opposing groups of dynamic processes: those which favour the formation of thrombin and fibrin, such as Factors V and VII, calcium ions and other activators and accelerators; and those which prevail against the formation of thrombin and fibrin, such as heparin, antithromboplastin and other inhibitors, those or/which dispose of formed fibrin, such as the fibrinolytic system. Both these groups of processes can be influenced in vivo by hormones, although there is no evidence that the incidence of thrombosis is increased in endocrine disorders.

Adrenaline and experimentally-induced stress accelerate clotting (Mills et al, 1928), increase prothrombin concentration (Uvnas, 1942; Leibetseder, 1951), and decrease heparin activity (Constantini and Tintori, 1951; Donzelot and Kaufmann, 1952). The administration of ACTH and cortisone during treatment of various collagen diseases has been associated with shortening of the clotting time and of the heparin-/
heparin-retarded clotting time (Cosgriff et al., 1950), and an increase in the incidence of thromboembolic episodes in such patients (Cosgriff, 1951). In certain animals shortening of the bleeding time followed experimental stress ACTH and cortisone, yet similar stress failed to influence the bleeding time after hypophysectomy or after adrenalectomy (Ungar, 1945), these observations suggest that the pituitary and adrenal cortex can both influence bleeding time; however, in man cortisone shortens prolonged bleeding time (Jacobson, 1953). The clotting mechanism may be partly under neurogenic influence as adrenergic stimuli increase and cholinergic stimuli decrease the tendency to thrombosis (de Takats, 1944); it may be that post-operative thrombosis is an extreme example of this increase in haemostasis following stress. The administration of growth hormone to dogs decreased the clotting time and prothrombin time (Campbell, 1953).

b. Fibrinolysis

Indirect testing of the efficiency of the fibrinolytic system by the intravenous administration of thrombin to rats suggested that ACTH and/
and cortisone inhibit fibrinolytic activity, and that growth hormone, TSH, desoxycorticosterone acetate and testosterone increase fibrinolytic activity (Ungar, 1954). Stefanini and Damashek (1955) have confirmed that ACTH and cortisone decrease fibrinolysis, yet experimental stress and adrenaline increase fibrinolytic activity (Macfarlane & Biggs, 1946; Biggs et al., 1947).

3. The influence of hormones on the arterial wall.

Any agent which increases the hypertonicity of arteries by producing contraction of the muscular elements in the arterial wall reduces the vascular bed and necessitates a compensatory acceleration of blood flow and an increase in dynamic pressure. Moreover, prolonged and inordinate vasoconstriction results in compression of the vasa vasorum by the contracting media with ischaemia of the arterial wall, particularly the inner layers, and the increased density of the contracted arterial wall may also hinder the normal diffusion of tissue fluids. Compression or active constriction of the capillaries within the arterial wall can result in local anoxaemia, which will alter the/
the normal tissue metabolism and may act as an nidus for accumulation of fat and lead ultimately to an atheromatus lesion.

a. Vasomotor tone.

Prolonged arterial hypertonicity can lead to clinical hypertension, and the positive correlation between hypertension and coronary disease, particularly in women, is well known (Davis and Klainer, 1940; Master, 1953). Certain hormones increase vasomotor tone and, although it is probable that the hypertension of Cushing's disease is largely related to the associated renal disease rather than the excessive secretion of adrenal steroids, one of the secretions of the adrenal cortex probably has a definite vasopressor action. Desoxycorticosterone can reasonably be regarded as a synthetic substitute for part of the adrenal cortical secretions, and experimentally it and the natural mineralocorticoid, 17-desoxocortisone, induce hypertension and hyaline changes in the arterial wall (Selye, 1950); however, aldosterone is said to lower vascular tone (Mach and Fabre, 1955). In view of the vasodilating action of oestrogens,
oestrogens, their withdrawal at the menopause has been implicated as a cause for the not uncommon development of hypertension and peripheral vascular insufficiency at the menopause (Scherf, 1940). Adrenaline and noradrenaline cause elevation of the blood pressure through their powerful vasoconstricting action; vasoconstriction occurs in the renal, splanchnic and cerebral arteries, but vasodilation takes place in the coronary arteries. In 1903 Josué produced degenerative lesions in the aortae of rabbits after repeated injections of adrenaline; many investigators have confirmed this observation and similar but more chronic arterial lesions, principally fibrous in character, develop in the coronary arteries as well as other arteries after the administration of small daily doses of adrenaline (Lange, 1924).

b. Capillaries.

Whereas adrenaline increases vasomotor tone, arterial lesions may be partly due to constriction of the capillaries supplying the arterial wall. An increase in capillary resistance occurs after the application of various forms of stress and after the administration of ACTH/
ACTH and insulin, and it has been suggested that this increase in capillary resistance may be due to stimulation of adrenocortical activity (Robson & Duthie, 1950). Adrenalectomy in rats is followed by reduction of capillary resistance, which can subsequently be restored by cortisone (Kramar and Simy-Kramar, 1953). ACTH and cortisone also decrease capillary permeability and fibroblast activity, and thereby impair organisation of intravascular thrombi and minor injuries of the arterial intima (Payling-Wright, 1954; Wang et al, 1955). Capillary permeability is increased in myxoedema and thyroxine therapy restores it rapidly to normal (Lange, 1944). In addition to producing changes in the arterial wall it has long been observed that myxoedema is associated with marked degenerative changes in the muscle fibres of the myocardium (Ord, 1880).

C. CONCLUSION.

1. The main proposition of this thesis.

The association of abnormalities of cholesterol metabolism, the coagulation system and the arterial wall with the development of coronary/
coronary atherosclerosis and ischaemic heart disease has already been emphasised. Frank endocrine diseases and the administration of hormones can influence cholesterol metabolism, the fluid state of the blood and metabolism in the arterial wall, and it is postulated that the normal homeostasis of these three processes could be disturbed by alteration of the physiological endocrine balance. The thesis is proposed, therefore, that an endocrine imbalance could contribute to the development of coronary atherosclerosis and ischaemic heart disease.

The principle weakness of this thesis lies in the fact that no marked and consistent abnormality of endocrine gland function has yet been found in patients who have the clinical features of coronary disease. It is unlikely that there is any gross endocrine disturbance in coronary atherogenesis as this would have wide metabolic repercussions and would have been recognised years ago, and it is possible that a comparatively minor disturbance may have passed largely unnoticed due to the crudeness of the available methods for assessing the function of the endocrine glands. However, there is some suggestive evidence that endocrine function may not be entirely normal in patients with ischaemic heart disease.

The/
The basal metabolic rate was lower than normal in a group of patients who developed ischaemic heart disease under the age of 40, and it was concluded that their thyroid function might be slightly depressed (Lerman & White, 1946); this observation has received confirmation recently (Gertler et al., 1953), but there was no significant difference in radioactive iodine excretion between coronary patients and euthyroid subjects.

The concentration of circulating protein-bound iodine decreases with advancing age (Perlmutter & Riggs, 1949), but no clear correlation has been found between protein-bound iodine levels and coronary disease (Tucker & Keys, 1951) although Marmorston et al. (1955) found a greater depression of circulating protein-bound iodine in post-menopausal women with myocardial infarcts when compared with healthy postmenopausal controls.

The relative freedom of premenopausal women from ischaemic heart disease is probably related to the endocrine differences between the sexes (see Pages 37, 92), and it is interesting to find that 30% of women who developed ischaemic heart disease before the age of 40 had some endocrine/
endocrine disturbance (Table XV). In view of the sex difference in the incidence of ischaemic heart disease and the depressant action of oestrogens on the circulating cholesterol, it might be expected that women who develop a myocardial infarct would excrete less oestrogen than a comparable control group, and biological determination of urinary oestrogen have indicated that this is so in two such groups of postmenopausal women (Marmorston et al, 1955). When Dr. Bauld worked in the Department of Biochemistry at Edinburgh University, he started to estimate the urinary excretion of oestrogens in healthy men and men with ischaemic heart disease. These investigations (Bauld et al, 1956) suggested that, in response to an injection of estradiol-17β, the ratio of oestriol to oestrone was significantly elevated in men after myocardial infarction when contrasted with healthy men, although the total excretion of oestrogens was unchanged. This difference was not observed in 3 men, who did not have a myocardial infarct but were suspected of having clinical coronary disease. These two studies suggest that oestrogen metabolism might be/
be disturbed in some patients with ischaemic heart disease. The proneness of males to ischaemic heart disease has led to an attempt to assess masculinity in such patients. Men who develop ischaemic heart disease under the age of 40 were considered to be morphologically more masculine than healthy men, but there was no consistent or significant difference in the excretion of 17-ketosteroids nor was there any correlation between the circulating cholesterol levels and the 17-ketosteroid excretion (Gertler et al, 1953). Blood and urinary corticoid levels have not been reported in patients with ischaemic heart disease except immediately after an acute myocardial infarct.

Thus endocrine gland function has not been carefully investigated in patients with angina and in patients who have recovered from a myocardial infarct; and, at present, the evidence obtained from standard tests of endocrine function is not adequate to refute or confirm the thesis that an endocrine imbalance might contribute to the development of coronary atherosclerosis.

2. The aetiology of ischaemic heart disease.
By 1955 20% of all the deaths in Great Britain were due to arteriosclerotic or coronary heart disease and the crude death rate from ischaemic heart disease had increased seventyfold in half as many years, yet before this century angina was a rarity and coronary thrombosis had been diagnosed only once during life. There is good reason to believe that this remarkable change in the statistics of the disease represents a real increase in its prevalence, and attention must be directed, therefore, towards potentially deleterious influences which have developed during this century. There have been fundamental and far-reaching social and economic changes. The standard of living of the civilised nations has never been higher and has resulted in an abundance of food not previously experienced. Industrialisation and world wars have revolutionised all our lives, and have created a new sense of strain and urgency and new responsibilities which many find difficult to withstand.

a. Diet.

In general, the intake of calories, protein and fat have increased with the rise in purchasing power which has followed the improvement
in the standard of living during this century. It is probably true to say that the physical activity and energy expenditure of many people has been reduced. There is now greater energy intake and less energy expenditure, and if energy intake exceeds energy expenditure, it is axiomatic that calories must be stored within the organism. Conservation of calories is most economically achieved by storing fat, which is deposited in many sites probably including the liver and arteries. When the intake of dietary calories is frequently in excess of the expenditure of calories by physical activity, a chronic disturbance of lipid metabolism might result.

In countries where the incidence of ischaemic heart disease is low, the contribution of fat to total caloric intake is also low. As the percentage of calories derived from fat increases from the poorer to the richer nations so the incidence of ischaemic heart disease increases, and elaborate epidemiological surveys indicate a positive correlation between the social and geographic incidence of ischaemic heart disease with the consumption of fat (Keys and Anderson, 1954; Keys et al, 1955; Bronte-Stewart et al, 1955). In most civilised communities more than one-third of the total caloric/
138.
caloric intake is derived from fat, and it is possible that this habitual daily ingestion of large quantities of fat, particularly if mostly from animal sources, may disturb the homeostasis of lipid metabolism and favour the development of coronary atherosclerosis and of ischaemic heart disease; when the diet contains excessive fat the levels of the circulating lipids and \( \beta \)-lipoproteins rise (Anderson and Keys, 1953; Keys et al, 1955) and there is more frequent and greater development of postprandial lipoaemia, which can accelerate blood coagulation (Fullerton et al, 1953; Poole, 1955; Robinson and Poole, 1956) and inhibit fibrinolysis (Greig, 1956).

b. Environmental "stress".

Even in countries where the fat consumption is high, most of the population fortunately does not suffer from ischaemic heart disease; of 5 men, whose environment and responsibilities are apparently closely comparable, only one may be expected to develop ischaemic heart disease. There is, then, an individual susceptibility, which is not well understood, but may be partly determined by heredity. The incidence of ischaemic heart disease/
disease is greatest in executive, professional, business and intellectual occupations, where heavy responsibilities often demand exacting and prolonged mental work (Ryle & Russell, 1949; Registrar-General for Scotland 1949-1953; Report of Oslo Life Insurance Companies, 1956) (Fig. 36). The psychological strain and emotional tensions that often accompany these responsibilities are undoubtedly stressful to some people, particularly if they have inherited an ambitious and conscientious personality, whereas others appear to be able to adapt themselves without undue difficulty. For example, the failure of certain inadequate personalities to adapt themselves to the environment can result in excessive appetite and disturbance of lipid metabolism with subsequent obesity (Hamburger, 1951; Brosin, 1954); this psychological production of obesity is probably mediated through the hypothalamus, which plays an important role in the control of appetite (Clark et al, 1938; Hetherington and Ranson, 1940). In general, it is probably true to say that during this century competition has been keener and incentives have been fewer, and personal/
Fig. 36. The distribution of deaths from ischaemic heart disease between the social classes (R. G. for Scotland).
personal financial and emotional stability has been less well balanced. Exactly what relation these changing environmental influences might have to the rapid development of ischaemic heart disease is at present obscure, but they should not be overlooked as aetiological factors of potential importance.

c. **Endocrine imbalance.**

It has already been postulated that an endocrine imbalance may favour the development of ischaemic heart disease and now some of the possible disturbances of normal endocrine balance will be considered. The nature and precision of each individual's endocrine balance may well be determined constitutionally and by heredity, and some individuals may be more susceptible than others to extraneous influences which tend to disturb this balance. Any primary endocrine dysfunction and particularly gross endocrine diseases will disturb the physiological hormonal balance. Failure to withstand environmental responsibilities might be transmitted to the endocrine system by way of the cerebral cortex and hypothalamus and result in disturbance of normal endocrine balance. Certainly acute "stress"
"stress" can lead to profound endocrine disturbances. For example, the normal pituitary-adrenocortical balance can be upset and lead to the various manifestations of the so-called "alarm reaction", such as hypoglycaemia, gastrointestinal erosions, haemoconcentration and eosinopenia; the normal pituitary-thyroid balance can be upset by acute psychic stress, and the rapid development of thyrotoxicosis following a sudden severe shock or acute anxiety is common and well recognised; similarly, the normal pituitary-gonadal balance can also be upset by acute psychological duress, and the sudden cessation of menstruation following extreme emotional anxiety has often been described. Thus, the relationship between "stress" and disturbance of endocrine gland function might be close, and future investigations may indicate that the aetiopathological role, which has been postulated in this thesis, of an endocrine imbalance in the production of ischaemic heart disease could be partly dependent on increasing environmental "stress" and decreasing ability to cope with it. 

d./
d. Ageing and local dynamic factors.

Ageing and local dynamic factors are undoubtedly very important in the production of ischaemic heart disease, but there is nothing to suggest that they now have a greater influence on the development of coronary atheroma than they did thirty and forty years ago when ischaemic heart disease was uncommon; moreover, there is no satisfactory evidence that the incidence of coronary atheroma has increased. Advancing age results in progressive loss of elasticity leading to dilatation and stretching of the arterial wall. This gradual deterioration with age is something which elastic tissue has in common with many similar colloidal substances, and maybe the starting point of most of the changes which occur with ageing (Ophüls, 1933). From early youth there is a tendency to splitting of the internal elastic lamina; at first this is not very marked but it becomes more and more complete with advancing age. Lansing (1955) has shown that the aminoacid composition of young and old arterial elastin is significantly different.
Subintimal anoxaemia, fibrosis, lipid deposition and calcification can occur in arteries as a result of many local influences including differences in intimal thickness, elasticity tortuosity and intraluminal hydrostatic pressure.

The possible aetiological relationship of diet, environment, endocrine imbalance and ageing is summarised in Fig. 37.
Fig. 37. A speculative scheme showing some of the possible relationships between various aetiological factors which favour the development of ischaemic heart disease.
PART IV.

THERAPEUTIC IMPLICATIONS

A. THE TREATMENT OF HYPERCHOLESTEROLAEMIA. 146

1. Diet 147
2. Hormones 152
3. Miscellaneous 166

B. CONCLUSION. 167
The presence and significance of abnormality of the circulating lipids and lipoproteins in patients with ischaemic heart disease have already been described (Part II). The blood coagulation and fibrinolytic systems and the tonic and metabolic functions of the arterial walls may also be disturbed in patients who are prone to develop coronary atherosclerosis with subsequent ischaemic heart disease. It may be very important to prevent the deposition of microscopic films of fibrin on the arterial intima and to improve oxygenation to the arterial wall, but at present so little is known about these disturbances that no therapy can be devised to correct them. Anticoagulants are effective against the formation of frank intravascular thrombosis, but even this action is not entirely straightforward; for instance, anticoagulants which cause hypoprothrombinaemia do not appear to retard clotting in vitro or in vivo (Wessler, 1953) and may achieve reduction in the incidence of thromboembolic episodes through some other action in addition to their anticoagulant properties (Gilchrist, 1952; Gilchrist & Tulloch/)
Tulloch, 1956). It has already been indicated that the abnormalities of blood coagulation and the disturbance within the arterial wall may be partially dependent on the presence of abnormalities in the circulating lipids and lipoproteins, and this section on therapy will, therefore, be concerned solely with the desirability and the possibilities of correction of these abnormalities.

A. THE TREATMENT OF HYPERCHOLESTEROLAEMIA.

It would seem reasonable to assume that reduction of the cholesterol in the plasma might result in the passage of less cholesterol along with the physiological diffusion of crystalloids and colloids from the arterial lumen through the arterial wall to the veins and lymphatics of the adventitia. In the experimental animal the degree and extent of cholesterol deposition in the arterial wall is directly proportional to the degree of hypercholesterolaemia, thus reduction of hypercholesterolaemia is followed experimentally by less cholesterol deposition. Similarly, any improvement in the stability of the colloidal dispersion of cholesterol in the plasma probably also results in a decreased tendency for cholesterol deposition.
deposition. Such stability depends on the inter-
relationship of cholesterol with other lipids,
particularly the phospholipids, and with protein
(see Pages 48 - 50); thus reduction of an
elevated C/P ratio and of an elevated \( \beta : \alpha \)
lipoprotein ratio might be regarded as desirable.
Lipaemia can accelerate coagulation and inhibit
fibrinolysis, and therefore correction of excessive
and frequent episodes of lipaemia might also be
beneficial.

1. Diet.

Consideration of some of the causes which
could disturb the normal circulating lipids and
lipoproteins and contribute also to the increasing
incidence of ischaemic heart disease has implicated
dietary fat (see Page 136), and restriction of the
daily fat intake would therefore seem logical. A
diet which is deficient only in cholesterol does
not produce any significant reduction of the elevated
circulating lipids and lipoproteins, but a diet low
in fat lowers these values.

a. Low fat diet.

Twelve hypercholesterolaemic men have been
studied over 4 years: 8 had had a myocardial
infarct, 2 had angina and 2 were siblings of
hypercholesterolaemic/
hypercholesterolaemic patients with coronary disease. Two of the men, who had had a myocardial infarct, died during the period of study and the results reported in Fig. 38 have been obtained from the remaining 10 men. These subjects were selected as intelligent and cooperative men whose sedentary occupations would not demand a high caloric intake. It was appreciated from the start that a low fat diet would be unpalatable, monotonous and difficult to observe strictly, and so a small group of cooperative men, mostly in clerical occupations, were selected in preference to a larger and more varied group. The initial daily regime consisted of 1200 calories with 20 g. of fat, or 15% of the total calories from fat. After 6 months this was increased in 7 men to 1600 calories with 26 g. of fat, which also represents 15% of the total calories from fat. One of the remaining 3 men received 1400 calories and 24 g. of fat, and the other 2 men received 1800 calories with 30 g. of fat. Thus, although there was some variation in the caloric intake, the contribution of fat never exceeded 15% of the total. These men have been/
The mean changes in the circulating lipids following the ingestion of a low fat diet by 10 hypercholesterolaemic men with ischaemic heart disease. The average intake was approximately 1400 calories and less than 25 g. of fat; during the last year the diets may have been rather more liberal in calories but have never exceeded 2000 and more than 15% from fat.
been followed at 3 monthly intervals and it is believed that, while there may have been occasional lapses, they have observed their diets strictly. From Fig. 38 it can be seen that there was an initial rapid fall in plasma cholesterol and at the nadir this was associated with ketonuria, presumably indicating some endogenous mobilisation of fat reserves. This harsh dietary regime eventually achieved no more than a 15% reduction in plasma cholesterol. Even if more complete removal of fat from the diet could be tolerated for any length of time, no very striking reduction of plasma cholesterol would be expected as cholesterol is synthesised in the liver from active acetate derived from all three dietary elements, protein, carbohydrate and fat (see Page 51). A totally fat-free rice-fruit diet will, however, achieve marked reduction of plasma cholesterol (Kempner, 1948).

It is concluded that severe restriction of dietary fat is unpleasant and often intolerable and does not achieve great reduction of the circulating lipids and lipoproteins, although dramatic effects can sometimes be achieved (Fig. 39).
Fig. 39. The changes in the circulating lipids and lipoproteins following the ingestion of a low fat diet by a patient with "idiopathic" hypercholesterolaemia and hyperlipaemia.
In 1955 the average man in Great Britain received 40% of his calories from fat, and it is possible that less severe restriction of fat to between 25% and 30% of the caloric intake might be more practical and might achieve slight reduction of the circulating lipids and lipoproteins.

b. **Vegetable oil diet.**

Evidence has been accumulating recently that an increase in the intake of vegetable fat causes depression of the circulating cholesterol, C/P ratio and \( \beta \)-lipoprotein cholesterol (Kinsell et al, 1952, 1953; Beveridge et al, 1955; Malmros and Wigand, 1955; Bronte-Stewart et al, 1956). It appears that this effect of vegetable and fish oils is roughly but directly proportional to their lack of saturation and is probably related to their essential fatty acid content. Whereas this effect of vegetable oils may lead to a practical therapeutic regime, at present an elaborate dietetic organisation is necessary to disguise the large quantity (200g) of oily emulsion which has to be swallowed each day. So far the author has not administered any vegetable oil to hypercholesterolaemic subjects but
the administration of sunflower seed oil, which acted as a severe stomach and bowel irritant, to healthy young men did not induce any significant depression of cholesterol below normal levels.

c. **Plant Sterols.**

Sitosterol, a stereoisomer of cholesterol, reduces the absorption of cholesterol from the diet and the reabsorption of cholesterol excreted in the bile; this effect may be achieved by competition for esterification which is necessary for the absorption of most intestinal cholesterol. The administration of sitosterol is followed by some reduction in circulating cholesterol in most hypercholesterolaemic patients (Pollak, 1953). The daily oral administration of 10 g. of \( \beta \)-sitosterol for 14 days to 4 hypercholesterolaemic men with coronary disease produced depression of the level of the circulating cholesterol by 10% and of the \( \beta \)-lipoprotein cholesterol by 8%. Sitosterol is a tasteless bran-like powder, which has to be sprinkled over all food making it dry and unpalatable. Plant sterols do not impair the absorption of carbohydrate and protein, and the endogenous synthesis of cholesterol is also unlikely to be affected. It is improbable, therefore, that/
that plant sterols will have any useful therapeutic application.

d. **Lipotrophic factors.**

Lipotrophic factors, such as choline and methionine, prevent fatty livers and are said to promote phospholipid synthesis thereby improving the transport and stability of cholesterol. Despite individual reports to the contrary, there has been no satisfactory evidence that they influence the circulating cholesterol in man (Davidson, 1951). The daily oral administration of 3 g. of choline chloride for 2 weeks to 6 hypercholesterolaemic patients with ischaemic heart disease did not result in any significant change in the plasma cholesterol or C/P ratio.

2. **Hormones.**

Three groups of hormones have been shown to lower hypercholesterolaemia; they are pituitary-adrenocortical hormones (ACTH and cortisone), thyroid hormones and the oestrogenic sex hormones. Since ACTH and cortisone have fundamental and widespread metabolic actions in addition to their action on circulating cholesterol, they are obviously precluded from any attempt to achieve/
achieve permanent reduction of hypercholesterolaemia. Thyroid hormones and the oestrogenic sex hormones have not been administered for the control of hypercholesterolaemia in many centres outside Edinburgh, and thus they will be considered in some detail.

a. **Thyroid hormones.**

The plasma cholesterol, C/P ratio and \( \beta \)-lipoprotein cholesterol are all significantly depressed during administration of \( \ell \)-thyroxine sodium, \( \ell \)-triiodothyronine and triiodothyroacetic acid (triac) to euthyroid hypercholesterolaemic men with coronary disease; this influence of these thyroid derivatives has already been considered in detail (see Pages 115 - 119). Unfortunately thyroxine itself and these analogues of thyroxine increase the basal metabolic rate and thus increase the work and oxygen consumption of the myocardium. When the blood supply is impaired by coronary atherosclerosis, any increase in the demands by the myocardium might be expected to result in temporary ischaemia and thus several of the men developed angina. This aspect of therapy with thyroxine derivative will now be discussed.

i. **Thyroxine.*/
i. Thyroxine.

It has already been reported that 6 euthyroid hypercholesterolaemic men with coronary disease received 600 μg. of l-thyroxine sodium daily for 2 weeks with depression of the circulating lipids and lipoproteins and concomitant elevation of the basal metabolic rate by a mean of +13% (see Fig. 24). Three of these men experienced appreciable reduction of their exercise tolerance due to the development of effort angina, which regressed completely a few weeks after thyroxine had been discontinued.

ii. Triiodothyronine

Three euthyroid hypercholesterolaemic men with coronary disease received up to 100 μg. of l-triiodothyronine daily for 6 weeks with depression of the circulating lipids and lipoproteins and concomitant elevation of the basal metabolic rate by a mean of +11% (see Fig. 25). Two of these 3 men experienced significant increase in the frequency of angina with subsequent regression when they received identical placebo tablets.

A further 3 euthyroid hypercholesterol-aemic men with coronary disease received up to 60 μg./
60 μg. of l-triiodothyronine daily over 7 weeks with depression of the circulating lipids and lipoproteins without any increase in basal metabolic rate (see Fig. 40). However, one man who had previously had an excellent exercise tolerance developed effort angina for the first time in 3 years; he had no rise in basal metabolic rate.

iii. Triiodothyroacetic acid.

Six euthyroid hypercholesterolaemic men with coronary disease received from 0.5 mg. to 4 mg. of triac daily over 95 days with depression of the circulating lipids and lipoproteins above a dose of 3 mg. (see Fig. 26). In two men there was elevation of the basal metabolic rate by 20\% and 13\% respectively. One of these two men and one of the remaining four men, in whom there was no elevation of basal metabolic rate, complained of marked reduction of exercise tolerance due to effort angina. When triac was withdrawn and placebo tablets started both these men experienced rapid regression of their symptoms and soon returned to their normal exercise tolerance.

A further 6 euthyroid hypercholesterolaemic men with coronary disease received from 3.0/
Fig. 40. The changes in the circulating lipids and lipoproteins, and in the weight and basal metabolic rate, during the oral administration of 40 and 60 µg. of \(t\)-triiodothyronine daily to 3 euthyroid hypercholesterolaemic men with ischaemic heart disease.
3.0 to 5.0 mg. of triac daily over 12 weeks with depression of the plasma cholesterol, C/P ratio and β-lipoprotein cholesterol at the 3 and 4 mg. dose levels (see Fig. 41). Despite the continued administration of 4 mg. of triac daily these values rose to the control levels, but there was a further slight fall when 5 mg. was administered daily although this was much less impressive than the original fall. Withdrawal of triac resulted in a rebound rise in the lipid and lipoproteins. The basal metabolic rate of these men was not significant altered, but one of these 6 men developed more angina and exertional breathlessness with reduction of exercise tolerance (Oliver & Boyd, 1957).

In summary, 24 euthyroid hypercholesterolaemic men with coronary disease, received thyroxine or one of its analogues. The circulating lipids and lipoproteins of them all were significantly lowered but 9 experienced definite reduction of exercise tolerance. This is readily understandable in 6 men, whose basal metabolic rates were elevated, but less so in the remaining 3 men, in whom there was no elevation of basal metabolic rate. It is interesting, and possibly important therapeutically, that the circulating lipids and lipoproteins/
Fig. 41. The changes in the circulating lipids and lipoproteins, and in the basal metabolic rate and weight, during the oral administration of increasing large doses of triiodothyroacetic acid to 6 hypercholesterolaemic euthyroid men with ischaemic heart disease.
lipoproteins can be lowered by small doses of triiodothyronine and triiodothyroacetic acid without elevation of the basal metabolic rate (Figs. 26, 40 and 41). It has been demonstrated in rats that triac increases the oxygen uptake of heart tissue to a greater extent than that of liver, skeletal muscle and kidney (Barker & Lewis, 1956; Boyd & Oliver, 1957). The measurement of the basal metabolic rate cannot reflect the relative oxygen requirements of all the body tissues and hence the administration of a substance, which produces a biological response (plasma cholesterol depression) without influencing the basal metabolic rate, may well alter the oxygen requirement of certain specific tissues. It is possible, therefore, that the dissociation of the action of triac on the circulating lipids and lipoproteins from any effect on the basal metabolic rate is more apparent than real, and may depend partly on inadequacy of the basal metabolic rate measurement to reflect a selective increase in the oxygen requirements of a comparatively small tissue. Triac not only induced angina but also failed to maintain depression of the/
the circulating lipids and lipoproteins despite increasing doses (Fig. 41). It is concluded that it is unlikely that triiodothyronine or triac, despite their insignificant action on the basal metabolic rate, will prove suitable for the long-term control of hypercholesterolaemia in patients with clinical coronary disease. Future investigations should be directed towards the discovery of a thyroxine analogue which will not only depress the circulating lipids without altering the overall metabolic rate but also will not cause angina or any selective increase in oxygen uptake by heart tissue.

b. Oestrogenic sex hormones.

It has already been shown that the plasma cholesterol, the C/P ratio and the \( \beta \)-lipoprotein cholesterol are all significantly and consistently depressed during the administration of any oestrogen (see Pages 119 - 122). Ethinyl oestradiol produced the most significant depression of the circulating lipids and lipoproteins. The vast majority of the 125 men, who have received oestrogens, have experienced gynaecomastia in varying degree, and in 2 of these men it was severe enough to cause withdrawal of the oestrogen preparation.
Depression of libido and loss of libido in older men occurred in 42% and nausea occurred occasionally. The frequency of these side effects of oestrogen therapy are listed in Table XXV.

Table XXV. The side effects of oestrogen therapy in 125 hypercholesterolaemic men with coronary disease.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Percentage of men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynaecomastia</td>
<td>98%</td>
</tr>
<tr>
<td>Depression or loss of libido</td>
<td>42%</td>
</tr>
<tr>
<td>Nausea</td>
<td>12%</td>
</tr>
<tr>
<td>Penile irritation</td>
<td>3%</td>
</tr>
<tr>
<td>Testicular pain</td>
<td>3%</td>
</tr>
</tbody>
</table>

Despite the frequency of gynaecomastia and depression of libido it is remarkable how well two of these/feminising effects have been tolerated. An attempt was made to minimise these feminising effects by the combined administration of an androgen or a progestin with ethinyl oestradiol.

i. Androgen and oestrogen.

(1) Methyl testosterone + ethinyl oestradiol:

12 hypercholesterolaemic men with proven coronary disease were studied over 68 weeks.

5 mg. of methyl testosterone were administered sublingually/
sublingually each day for 4 weeks, and 10 mg for a further 4 weeks. During these 8 weeks the men also received inert tablets similar in size and shape to ethinyl oestradiol. At the end of 8 weeks tablets containing 400 μg. of ethinyl oestradiol were substituted for the inert tablets, and for the next 14 weeks the men received increasing doses of ethinyl oestradiol and 10 mg of methyl testosterone daily; after the first 2 weeks 600 μg. of ethinyl oestradiol were administered each day and after 2 more weeks 800 μg. then after 2 further weeks 1 mg. of ethinyl oestradiol was administered daily. At the end of 14 weeks combined therapy inert sublingual tablets identical to the androgen were substituted, and the men received 1 mg. of ethinyl oestradiol daily for 4 more weeks when identical inert tablets were again substituted for the oestrogen; the men then received two groups of inert tablets for a further 12 weeks.

The results of this study are shown in Fig. 42. The plasma cholesterol did not undergo any appreciable fall until a dose of 1 mg. of ethinyl oestradiol was reached, but when methyl testosterone/
Fig. 42. The changes in the circulating lipids during the combined oral administration of methyl testosterone and ethinyl oestradiol to 12 hypercholesterolaemic men with ischaemic heart disease.
testosterone was withdrawn, the plasma cholesterol fell by 21%. The C/P ratio did not undergo any appreciable fall until 800 μg. of ethinyl oestradiol was being received daily but when methyl testosterone was withdrawn, the C/P ratio fell by 23%.

(2) Ethinyl oestradiol + methyl testosterone.

A further 12 hypercholesterolaemic men with proven coronary disease were studied for 30 weeks. 200 μg. of ethinyl oestradiol were administered daily for 2 weeks, and thereafter up to the end of the 10th week the daily dose was increased by 200 μg. every 2 weeks. During these 10 weeks the men also receive inert sublingual tablets similar in size, shape and taste to methyl testosterone sublingual tablets. At the end of these 10 weeks sublingual tablets containing 20 mg. of methyl testosterone were substituted for the inert tablets, and for the next 4 weeks the men received the androgen and 1 mg. of ethinyl oestradiol daily. After 4 weeks combined therapy inert tablets identical to the oestrogen were substituted, and the men received 20 mg. of methyl testosterone daily for 4 more weeks/
weeks when inert sublingual tablets were again substituted for the androgen; the men then received two groups of inert tablets for a further 4 weeks.

The results of this study are shown in Fig. 43. The plasma cholesterol fell by 25% after 10 weeks of ethinyl oestradiol. When methyl testosterone was introduced, the plasma cholesterol rose by 35%, and when ethinyl oestradiol was withdrawn, the plasma cholesterol rose a further 12%. The C/P ratio fell by 25% after 10 weeks of ethinyl oestradiol. When methyl testosterone was introduced, the C/P ratio rose by 20%, and when ethinyl oestradiol was withdrawn, the C/P ratio rose a further 19%.

The administration of methyl testosterone in these two studies not only failed to modify or prevent any of the side effects of ethinyl oestradiol, but resulted in partial inhibition of the depressant action of ethinyl oestradiol on the circulating lipids.

ii. Progestin + oestrogen

Ethinyl testosterone + ethinyl oestradiol

12 hypercholesterolaemic men with proven coronary/
Fig. 43. The changes in the circulating lipids during the combined oral administration of ethinyl oestradiol and methyl testosterone to 12 hypercholesterolaemic men with ischaemic heart disease.
coronary disease were studied for 26 weeks. 20 mg. of ethinyl testosterone (anhydro-hydroxyprogesterone) were administered sublingually each day for 2 weeks; thereafter 40 mg. were administered daily for 2 weeks and then 60 mg. were administered daily for the next 2 weeks. During these 6 weeks the men also received inert tablets similar in size and shape to ethinyl oestradiol. At the end of 2 weeks, tablets containing ethinyl oestradiol 500 μg. were substituted for the inert tablets, and for the next 4 weeks the men received the oestrogen and 60 mg. of the progesterone analogue daily; after 2 weeks 1 mg. of ethinyl oestradiol was administered daily. At the end of 4 weeks of combined therapy inert sublingual tablets identical to the progesterone analogue were substituted, and the men received 1 mg. of ethinyl oestradiol daily for 2 more weeks when identical inert tablets were again substituted for the oestrogen; the men then received two groups of inert tablets for a further 8 weeks.

The results of this study are shown in Fig. 44/
Fig. 4. The changes in the circulating lipids during the combined oral administration of anhydrohydroxyprogesterone (ethinyl testosterone) and ethinyl oestradiol to 12 hypercholesterolaoemic men with ischaemic heart disease.
Fig. 44. The plasma cholesterol fell by 12% after 6 weeks of ethinyl testosterone. It fell by a further 10% when 1 mg. of ethinyl oestradiol was administered at the same time. There was a rise in plasma cholesterol by 18% when ethinyl testosterone was withdrawn even although the men were still receiving 1 mg. of ethinyl oestradiol daily, and there was a further rise on withdrawal of ethinyl oestradiol. The C/P ratio did not alter significantly during the 6 weeks when the men received ethinyl testosterone, but it fell by 13% when ethinyl oestradiol was introduced. The C/P ratio subsequently rose by 29% following withdrawal of ethinyl oestradiol. This combined administration of a progestin with ethinyl oestradiol failed to ameliorate any of the feminising side effects of oestrogen therapy.

In summary, there is no doubt that the oestrogenic sex hormones lower the abnormal circulating lipids and lipoprotein patterns present in clinical coronary disease, but their feminising actions are likely to preclude them from any attempt at long-term control of hypercholesterolaemic patients with clinical coronary disease. Nevertheless,
Nevertheless, a long-term study of the effect of oestrogens on the circulating lipids and on the rates or morbidity and mortality from ischaemic heart disease is being conducted. The subjects are 100 men with proven myocardial infarction; these men were discharged consecutively from Ward 22 of the Royal Infirmary and ever since alternate cases have received 200 μg. of ethinyl oestradiol daily or identical inert tablets. The men attended as outpatients every 3 months during the first year after discharge from the ward and have attended 6 monthly thereafter; the clinical features, blood pressure, weight and a blood specimen for lipid analysis have been assessed at each visit, and an electrocardiogram has been recorded at every second visit. The majority have been followed for 1½ years and 25 for more than 2 years. The effect of ethinyl oestradiol on the circulating lipids is shown in Fig. 45. In contrast to triiodothyroacetic acid, ethinyl oestradiol maintains depression of the plasma cholesterol and C/P ratio over long periods; the greater effect on the C/P ratio emphasises that oestrogens/
The changes in the circulating lipids during the oral administration of 200 
µg. of ethinyl oestradiol daily on a long-term basis. The number of cases in the control group and oestrogen treated group are also shown.
oestrogens cause elevation of the phospholipids as well as depression of cholesterol. Up to the present there have been 6 deaths in the oestrogen treated group and 4 deaths in the control group; it is unlikely that this study will give any reliable or valuable information concerning the influence of lowered circulating lipids on morbidity and mortality until it has been pursued for 5 years.

3. Miscellaneous.

Several miscellaneous substances such as large doses of heparin (Basu & Stewart, 1952), nicotinic acid (Altschul & Herman, 1955), chelating agents (Perry & Schroeder, 1955), and phenyl ethyl acetic acid (Mathivat & Cottet, 1953) have been reported to lower plasma cholesterol.

Phenyl ethyl acetic acid, or "hyposterol", has been administered at three dose levels to 18 hypercholesterolaemic men with proven coronary disease. No significant change was produced in 6 men during the daily oral administration of 1.2 g. (optimum dose according to the original investigators) for 12 weeks or in a further 6 men during the daily oral administration of 2.7 g. for/
The effect of phenyl ethyl acetic acid on the circulating lipids and lipoproteins in hypercholesterolaemic men with ischaemic heart disease.

<table>
<thead>
<tr>
<th>Dose (g./day)</th>
<th>Duration (weeks)</th>
<th>Number of subjects</th>
<th>Plasma cholesterol (%)</th>
<th>C/P ratio (%)</th>
<th>β-lipoprotein cholesterol (%)</th>
<th>α-lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>12</td>
<td>6</td>
<td>+8%</td>
<td>+13%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2.7</td>
<td>4</td>
<td>6</td>
<td>+11%</td>
<td>+4%</td>
<td>+3%</td>
<td>-7%</td>
</tr>
<tr>
<td>5.0</td>
<td>2</td>
<td>6</td>
<td>-17%</td>
<td>+7%</td>
<td>No significant change</td>
<td></td>
</tr>
</tbody>
</table>
for 4 weeks. However, the daily oral administration of 5g to a further 6 men resulted in slight depression of the mean plasma cholesterol by 17% (Table XXVI). Although apparently not toxic after a few weeks, phenyl ethyl acetic acid has not yet been administered over long periods. At present it is not regarded as a potent cholesterolytic agent.

B. CONCLUSION.

At present there is no really effective acceptable method of lowering hypercholesterolaemia. Restrictions or alterations of the diet are unpleasant and monotonous, and do not achieve any very marked or consistent depression of hypercholesterolaemia. Thyroid analogues and oestrogens achieve the most marked and consistent depression of the elevated circulating lipids and lipoproteins but the former increase myocardial metabolism even in the absence of any effect on the basal metabolic rate, and the latter induce feminisation to a greater or lesser degree in every subject. It is possible that intensive investigation of new thyroid analogues will lead to a derivative which will have little or no effect/
effect on metabolism but continue to depress cholesterol. It is also possible that a "non-feminising oestrogen" will be developed, although such a preparation may also lose its cholesterolytic action.

It is on a study of prognosis, and not on a study of reduction of circulating cholesterol that the efficiency of any particular regime must be judged. It is fundamental to determine whether correction of the abnormal circulating lipids and lipoproteins is associated with an improvement in morbidity and mortality, and particularly with inhibition or even regression of the atherosclerotic lesions. This is obviously difficult to investigate in man, although some indication that the atherosclerotic process might be halted is obtained from two recent studies. Autopsies of middle-aged men who died in Russian prisoner-of-war camps after months or years of extreme hunger, and autopsies of men who died during the hunger blockade of Leningrad in 1942 were remarkable for the frequent absence of any atherosclerosis in the coronary arteries and for the very rare occurrence of/
of significant atherosclerotic lesions; moreover, myocardial infarcts were practically never found (Pierach, 1955). Similarly, autopsies of men, who died from carcinoma of the prostate after receiving large doses of oestrogens, showed less coronary atherosclerosis than a comparable control group (Rivin & Dimitroff, 1953). It is encouraging to think that the atherosclerotic process might have been retarded in the subjects of these studies. Yet once atherosclerotic lesions have become extensive and severe enough to produce clinical features of ischaemic heart disease, inhibition of the atherosclerotic process may not necessarily prolong life; when an efficient and acceptable therapy can be proved to retard the atherosclerotic process in the human, it should probably be offered primarily to the younger and apparently healthy members of the community. Any such prophylactic regime will depend on the perfection of reliable tests so that those individuals who are likely to develop ischaemic heart disease can be selected with certainty from the healthy population.
SUMMARY

The early history, the nature and the incidence of coronary atherosclerosis and ischaemic heart disease have been reviewed. Evidence has been presented to suggest that there are aetiological factors which favour the development of ischaemic heart disease without influencing the incidence of coronary atherosclerosis.

The close relationship of cholesterol metabolism to coronary atherosclerosis and to ischaemic heart disease has been emphasised.

The circulating lipids and lipoproteins have been studied in health in relation to age and sex. They were abnormal in the majority of patients with ischaemic heart disease, particularly in those under the age of 50. Analysis of the circulating lipids and lipoproteins could aid the solution of an equivocal diagnosis in young subjects suspected of having ischaemic heart disease.
The effects of endogenous hormones and the action of administered hormones on the circulating lipids and lipoproteins have been described in detail. Hormones can also influence the fluid state of the blood and the tonicity and metabolism of arteries. It has been postulated that the homeostasis of cholesterol metabolism, of the fluid state of the blood and of arterial metabolism could be disturbed by alteration of the physiological endocrine balance.

The thesis has been proposed that an endocrine imbalance could contribute to the development of coronary atherosclerosis and of ischaemic heart disease. The relationship of this thesis to existing theories of the aetiology of ischaemic heart disease has been considered in detail.

Finally, some therapeutic implications of these metabolic and endocrine aspects of coronary disease have been considered.
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