Jens Møller

# Cholesterol

## Interactions with Testosterone and Cortisol in Cardiovascular Diseases

Foreword by Helge Einfeldt

With 4 Figures and 12 Color Photographs



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# Foreword

In 1935, Butenandt and Ruzicka received the Nobel Prize for synthesizing testosterone from cholesterol. Over the next few years, testosterone was used therapeutically by several clinicians, especially in Germany. However, with the outbreak of the Second World War, international scientific research was effectively brought to an end.

Using testosterone extracted from postmortem material, workers at the clinic of the famous Danish surgeon Thorkild Rovsing were able to show as early as the First World War that the substance had beneficial effects on cardiovascular disease. Given that this particularly important chapter in medical history opened in Copenhagen, it is appropriate that testosterone treatment was taken up in the 1950s by Jens Møller. During the 35 years since then, he has gained enormous experience in treating cardiovascular disease and is amply qualified to review the role testosterone has played in the more than ten thousand patients he has treated, most of them successfully. Many have even been saved the experience of amputation.

Drawing on authoritative sources and expert opinion in the fields of biochemistry and physiology, this book explains the scientific basis that underlies this achievement. It is a success I have seen personally in the course of several periods spent working with Møller in Copenhagen.

Since members of the European Parliament had expressed great interest in the problems posed by cardiovascular disease and in the possibilities for effective treatment and prevention, it was decided to hold a symposium in Strasbourg. The meeting, which took place in 1975, was led by an honorary committee composed of the following members:

Mr. Georges Spenale
President of the European Parliament

Mr. Finn D. Gundelach
Member of the Commission of the European Communities

Mr. Libero della Briotta
President of the Commission of Public Health
and Environment of the European Parliament

Mr. Christian Albertsen
Member of the Commission of Public Health
and Environment of the European Parliament

Mr. Pierre Pflimlin
Mayor of Strasbourg
(Former Prime Minister of France)

The scientists and parliamentarians who formed the symposium's audience agreed to establish the European Organization for the Control of Circulatory Diseases (EOCCD). At its inaugural General Assembly in 1976, Møller was

elected President, and myself General Secretary. Since 1976, the EOCCD has held symposia in a number of European cities, including London at the House of Lords (July 1977) and at the Royal College of Obstetricians and Gynecologists (June 1979), in Bonn (November 1978), in West Berlin (1982), and in Munich (1983 and 1985). Several meetings have been hosted by the European Parliament in Strasbourg and Luxembourg.

This book fulfills the promises made by Møller and me to the European and national parliaments, to produce a document which clarifies the problems posed by cardiovascular disease and provides a basis for testosterone treatment. It gives a scientific explanation of why an increased cholesterol level is a biological symptom of cardiovascular disease and shows how this level can be decreased by testosterone.

Helge Einfeldt

# Preface

The intention of this book is to elaborate on the contents of my first book *Testosterone Treatment of Cardiovascular Diseases*, which seems to have created a stir. The fact that areas of gangrene have been healed has attracted attention and surprised many readers. Let me emphasize that this kind of reaction justifies my endeavor to make this problem a topic of discussion to the benefit of the patients. I cannot of course expect the scientific basis of my theories to satisfy everyone. A critical attitude is a splendid encouragement for further investigation. To quote Professor B.R. Martin, Department of Biochemistry, University of Cambridge, "The biochemical aspects of your theories represent a well supported hypothesis. Like any useful hypothesis it raises some questions as I have tried to point out. This does not of course imply that the theory is invalid, if anything rather the contrary since one is always suspicious of a theory which raises no new questions."

Carruthers' call for action in this book is an incentive to continue the work already started.

I am grateful to the leading specialists in CVD research who took the initiative to come to my clinic in Copenhagen to witness the results of the treatment and assess the patient material. Professor William Boyd commented in his textbook *Pathology for the Physician* (1965):

> I personally have seen in Copenhagen a remarkable demonstration of the relief afforded by these measures (hormone therapy), in some cases saving the patient from amputation and even suicide.

Dr. Malcolm Carruthers, from the Maudsley Hospital, London, wrote in his report (1980) after his sabbatical leave at my Copenhagen clinic in 1978:

> Particularly impressive were the healing areas of gangrene and other regions of ischemic ulceration. Gangrene in one or several toes which, in most clinics, would have been treated by immediate amputation, dramatically improved with anabolic steroids and antibiotics. The blackened, necrotic areas became dry and less infected and within a few weeks separated, leaving a clean healing surface. Perhaps the most dramatic, from the patient's point of view, was the relief of pain associated with ischemic lesions. Impaired sleep for months or years often results in severe depression or being on the brink of suicide. Relief of the limb pains and restlessness at night, as well as allowing sleep, which makes the patient feel well to the point of euphoria, reduces the associated stress which may contribute to the sympathetic predominance initiating from the maintaining lesion. Around 25% of the patients presented symptoms of coronary insufficiency, varying from angina on effort to a history of recent myocardial infarction. A further 25%, though presenting symptoms predominantly affecting the limbs, admitted to a history of chest pain on exertion, or had ECG signs of cardiac ischemia either at rest or on exertion testing. This is a further proof of the multifocal nature of arterial disease. On anabolic steroids there was routinely remission of these symptoms and normalization of the S-T segment of the ECG was repeatedly observed.

Following their visit in 1979, a group from the Hammersmith Hospital (University of London) consisting of Consultant Endocrinologist C. F. Joplin, Consultant Vascular Surgeon C. W. Jamieson, and Professor of Cardiovascular Medicine C. P. Shillingford stated (Shillingford et al. 1980):

We were impressed by the healing of large and deeply penetrating ulcers in legs without foot pulses which we should not have expected to have healed in the normal course of events, but might have led to amputation of the limb.

Dr. Yarnell (1980) of the Medical Research Council stated:

At Dr. Møller's clinic in Copenhagen androgens have been used in the treatment of peripheral vascular disease for some 20 years. The clinic has an international reputation for clinical treatment. On my visit today I have seen 24 unselected patients aged from 30 to 82 years with peripheral vascular disorders who attended for follow-up. Documentary evidence was provided as to the extent of gangrene prior to treatment with anabolic steroids (usually testosterone in oil given i.m.). The results are impressive. Many patients have been spared amputation of fingers, toes, or whole limbs. Many of the initial lesions occurred many years ago and most patients have remained disease-free since initial treatment. As Dr. Møller points out, such treatment cannot give eternal life, but the personal testament of these patients is that this treatment provides a radical improvement in their quality of life.

Finally I am very grateful to those whose support and effort made possible the completion of this book. First and foremost I must mention Dr. Helge Einfeldt, the General Secretary of the EOCCD, whose organizational talents have been indispensable. He has conducted conferences and symposia in Germany which have been attended by scientists from around the world, and which have provided me an opportunity to present and further develop my theories on a firm ground. He has also been untiring in his efforts to obtain references to literature on this subject. I am profoundly grateful to him.

## Acknowledgement

Dr. Helge Einfeldt has been involved with my clinic for many years, concerning himself with both scientific and administrative matters. In 1970, he drew up a historical overview of the literature on the treatment of cardiovascular diseases with testosterone. This document has been a great inspiration for me in writing this book. His organizational talents are invaluable: he has been active in arranging symposia at the Danish Parliament, Christiansborg, on May 11, 1973, and October 19–20, 1973; at the *Maison de l'Europe* (European Parliament, Strasbourg) on June 20–21, 1975; in April 1976 in Luxemburg, where I was elected President and he was elected General Secretary of the European Organization for Control of Circulatory Diseases; on November 17, 1976, at the *Centre Européen*, Luxemburg; at the House of Lords in London on June 21–22, 1977; the *Palais d'Europe* in Strasbourg on December 15, 1977; in Bonn on November 9, 1978; in London on June 18, 1979; on November 9, 1981, in Berlin; on October 10, 1973, and on November 4, 1985, in Munich. At these congresses leading scientists in the fields of biochemistry and clinical medicine from all over the world gathered together to take part in discussions that have underscored the significance of the ideas expressed in this book.

I must also express my gratitude to Helge Einfeldt for his contribution to negotiations with Springer-Verlag in Heidelberg. His untiring efforts have given me indispensable support in the writing of this book.

# Contents

Cholesterol

For the last two decades, a controversy has raged between scientists over the role cholesterol plays in the causation of cardiovascular disease (CVD). This dispute, which has often taken on a bitter tone, still continues and has so far failed to produce any results beneficial to patients. In my opinion high cholesterol concentration is more a *symptom* of a deterioration in circulation than a factor causing CVD. This is certainly the case where raised cholesterol levels exist together with other pathological changes, and where all these abnormalities can be counteracted by an anabolic factor. I therefore oppose those scientists who consider an increased level of cholesterol to be *the cause* of CVD.

This book concerns the pathological changes that lead to an increase in cholesterol level and to CVD. In it I will try to show why it is possible to improve the deteriorated circulation and decrease the cholesterol level by the administration of testosterone. I have acted accordingly and obtained results beneficial to patients.

In my clinic, the plasma cholesterol concentration is measured before and after the treatment of CVD with testosterone. Therapy with this anabolic substance significantly decreases the cholesterol level. Parallel with my investigations, but independent of them, two university clinics in Denmark have shown the same effect. One example, from the hormone laboratory of the Copenhagen State Hospital, will serve as an illustration. Cholesterol concentrations were measured in the serum of 300 male patients, aged between 41 and 82, with clinically recognized circulatory disease. In 83% of these patients, cholesterol concentration fell during androgen treatment. On average, the level after testosterone was 74% of the pretreatment concentration. The extent to which cholesterol is reduced is independent of the level before treatment, since the decrease was no greater in the seven patients with the highest pretreatment levels than in the remainder of the group. I find that 74% of the pretreatment value is a very satisfying result. The study undertaken by the other university clinic will be mentioned later.

In its discussion of the various beneficial effects of anabolic steroids, a report from a World Health Organization (WHO) symposium held in Madrid in 1972 also provides evidence of the cholesterol-lowering effects of testosterone.

> A number of compounds are available which, when administered orally, raise and sustain the level of fibrinolytic activity significantly. Most successful in this regard are the anabolic steroids and the oral hypoglycaemic agents. Ethylestrenol and phenformin are the most active among the two groups and when used in combination they induce enhanced levels of fibrinolytic activity — approximately five times normal — which can be maintained for periods of several years without any experience of untoward consequences. This combination also produces a reduction of plasma fibrinogen of approximately 25 percent, a decrease in platelet adhesiveness, and a *significant fall in serum cholesterol.* (Emphasis added).

This report confirms my understanding of the phenomenon: by improving one parameter in CVD with testosterone, the others will follow — in this case fibrinolytic activity increases, platelet adhesiveness decreases, and cholesterol level is reduced by testosterone. I refer to my view as the cog-wheel theory and will

explain it later. We have already cited evidence that cholesterol reduction can be achieved by testosterone alone. Studies also show that the fibrinolytic effect is obtained when testosterone is administered without phenformin (Davidson et al. 1971). (See also Winther 1965 and many others; the subject of oral antidiabetics is discussed further in the section "Diabetic States and CVD".)

As stated by the WHO, testosterone normalizes all the variables mentioned above and causes a shift from anaerobic to aerobic metabolism. *Anaerobic metabolism*, i.e., CVD, means an increased cholesterol level, increased ADP concentration — resulting in increased platelet adhesiveness — and decreased fibrinolytic activity. *Aerobic metabolism*, i.e., normal circulation, means normal cholesterol level, normal ATP production — inhibiting platelet adhesiveness — and normal fibrinolytic activity.

It has always been a mystery to me why some scientists make such a point of using every opportunity to attack high levels of cholesterol which, I repeat, indicate deterioration in the circulation but are not its cause. In addition to cholesterol, there are many other fundamental, interdependent metabolic changes which, of necessity, must be effected if the circulation is to improve. Cholesterol is the precursor of many hormones, including the vital substance testosterone itself. Decreasing the cholesterol level alone may in fact result in a decrease in the production of testosterone, which plays an important role in maintaining a normal circulation.

Testosterone is a life-giving and life-maintaining substance. It has been suggested that cyclopentanoperhydrophenanthrene, the nucleus of the testosterone molecule, might have played a unique role in the evolution of life on earth. We know that testosterone promotes libido in both men and women, which is a necessity for the continuation of life. This libido effect and testosterone's role in the development of male sexual characteristics have resulted in it being called a sex hormone. Libido is psychological and subjectively conditioned and consequently beyond the range of the usual laboratory measurements. Unlike in animals, sexual functions in humans have become extensively encephalized and emancipated from hormonal control.

The anabolic effect of testosterone, on the other hand, is a biological and objective phenomenon, measurable in a variety of ways.

Protein is the core substance of our bodies. And since testosterone is responsible for the building of protein from the point of conception to our very last breath, its anabolic function is an absolute precondition for the maintenance of life. In this role, testosterone's effect is expressed equally in both sexes, as is the effect of prostaglandins, for example. Despite their names, neither of these substances is specifically male.

Investigations show that the endocrine secretion of the embryonic testes is the sole and decisive factor in the differentiation of male and female sexual characteristics. The embryonic ovary does not secrete hormones.[1]

I would prefer to call testosterone "the anabolic steroid" instead of "the male sex hormone." Testosterone has a role far wider than that of estrogen, and it therefore seems "unfair" to give it the status simply of a sex hormone.

The way in which testosterone stimulates protein synthesis is described by Bardin (1979):

> Once the androgen-receptor complex is formed, it is transferred to the nucleus where it binds to specific sites on chromatin. The binding site for the steroid-receptor complex has been termed the nuclear acceptor site. Interaction of the steroid-receptor complex with its receptor results in a striking increase in nuclear metabolism. This includes an increase in chromatin activity, an increase in the number of initiation sites on chromatin, and an increase in the synthesis of all classes of RNA. These events lead to increased transfer of RNA to cytoplasm, which results in protein synthesis, cellular growth and differentiated function.

Ganong (1975, pp 325-326) describes the same process:

> Androgens *increase* the synthesis and *decrease* the breakdown of protein, leading to an increase in the rate of growth....Androgen combines with a protein in the cell and brings about derepression of part of the genetic message, with the resultant formation of new mRNA and stimulation of protein synthesis. (Emphasis added)

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1 Estrogen is made from testosterone. Lehninger (1982) writes in his book *Principles of Biochemistry*, "The principal estrogen secreted by the human female is $\beta$-estradiol, made by the ovary, from, of all things, testosterone, the principal male sex hormone. Eve was made from more than Adam's rib!"

## Biochemical Relations Between Cholesterol, Testosterone, Cortisol, and Catecholamines

As a basis for further discussion of *the effect of testosterone on cholesterol*, and of its relevance to CVD, it is appropriate to describe the factors involved in aerobic and anaerobic metabolism in greater detail.

Under normal conditions of *aerobic metabolism*, pyruvic acid is oxidized in the Krebs cycle. Pyruvic acid is converted first to acetyl coenzyme A (CoA), which then combines with oxaloacetic acid to form citric acid. The conversion of citric acid to α-ketoglutaric acid to succinic acid and back to oxaloacetic acid (via numerous intermediaries) results in the formation of two molecules of water from each molecule of pyruvic acid. Altogether about 40 molecules of the high-energy substance ATP are synthesized from every glucose molecule broken down by aerobic dissimilation (Green 1976, p 112). By aerobic metabolism the ATP-ADP ratio is increased. This is important not only for adequate metabolism in, for instance, the myocardium but also because a fall in the ATP-ADP ratio stimulates platelet adhesiveness. Furthermore, normal ATP production means a normal level of cholesterol — an issue that will be dealt with later in this book.

Such metabolism exhibits a general equilibrium between anabolic and catabolic processes. In the organism, normal aerobic metabolism is correlated with a certain level of cholesterol. According to my theories, this level will rise if the metabolism in the same organism switches to the anaerobic mode (see the section on surgical stress).

*Cortisol* breaks down protein into amino acids which, after deamination, are built up into glycogen in the liver by appropriate liver enzymes, a process which is also activated by cortisol. The catecholamines break down glycogen to blood glucose which, under normal conditions, enters into the cell and into the Krebs cycle under the influence of insulin. Thus protein and carbohydrate metabolism are linked by cortisol and catecholamines, which have the effect of channeling the breakdown products of both substances down a final common pathway into the Krebs cycle. However, if cortisol and catecholamines are present in excess, they inhibit glucose uptake by the tissues and produce glucosuria and increased resistance to insulin (i.e., steroid diabetes, which is a fundamental feature of CVD). They also result in there being more acetyl CoA than can be matched by the available oxaloacetic acid — a state of anaerobic metabolism. In the prevailing anaerobic conditions, the result is condensation of excess acetate units to cholesterol.

The excess of cortisol which results in protein breakdown can be counteracted by the administration of *testosterone*. By promoting protein synthesis, testosterone diverts amino acids from glycogen to protein production and so counteracts anaerobic metabolism and benefits carbohydrate and aerobic metabolism. Furthermore, testosterone enhances dehydrogenase activity in the Krebs cycle (see, e.g., Janda et al. 1976) and increases the concentration of 2,3-diphosphoglycerate (DPG) (Ganong 1975), thereby improving the oxygen supply to the tissues. Through the normalization of carbohydrate metabolism and the reversal of

now sufficient oxaloacetic acid for the oxidation of acetyl CoA, *thus decreasing the cholesterol level.*

Opposing the action of testosterone is cortisol, which has the function of breaking down protein and, if in excess (together with catecholamines), impairs carbohydrate metabolism. Cholesterol is the precursor of both testosterone and cortisol. Therefore, cholesterol plays a crucial biochemical role. Within the triad of these substances — cholesterol, cortisol, and testosterone — there is a continuous struggle between testosterone and cortisol; *and the state of this struggle is reflected in the level of cholesterol.*

Life unfolds in protein. Protein is the living, respiring substance that needs to be fuelled and supplied with oxygen to sustain combustion and provide energy for the unique material that is life itself — performing physical activity, expressing itself in the actions of every enzyme, regulating each function of the body. Protein is the substance on which all the biochemical and physiological activity of life is based. And testosterone is the hormone whose major role is to build up this core substance.

From birth until the prime of life, the anabolic effect of testosterone on protein dominates the catabolic influence of cortisol. Around the prime of life there is equilibrium. From this age onwards we act as "cannibals," consuming our own bodies as the effect of cortisol gradually takes over. This process leads eventually to the extinction of life — if no accident or disease intervenes beforehand. However, certain situations that occur during life impose a particular stress on the body. This induces an ACTH-stimulated rise in cortisol production. The result is the breakdown of protein (and its conversion to carbohydrate) at a rate faster than would be normal for that age. This radical attack on the core substance of life may cause the inactivation of enzymes necessary for normal aerobic metabolism. At the same time there is an overproduction of catecholamines with all its metabolic effects, which is yet another aspect of the stress response.

As previously mentioned, an excess of catecholamines leads to anaerobic metabolism, impaired carbohydrate metabolism, and increased cholesterol level. If such departures from normal metabolism are repeated and are not compensated by natural homeostastic processes, a vicious circle is initiated. Cortisol excess, in association with the overproduction of catecholamines, leads to impaired carbohydrate metabolism, resulting in a surplus of acetyl CoA ($CH_3COOH$-CoA), which builds up more cholesterol. This in turn is converted into cortisol, and the cycle repeated. This vicious circle forms a basis for the development of CVD.

The level of *cholesterol*, the third substance in the triad, is related to the influence of the two other factors, testosterone and cortisol. Cholesterol excess arises from anaerobic metabolism and is not to be considered as a dietary problem. Indeed, cholesterol synthesis is actually *inhibited* by dietary cholesterol: the higher the intake in food, the lower the endogenous production (for example, Lehninger 1982, p 611). I see the effect in this way: an increased level of cholesterol is a biochemical phenomenon which should be corrected biochemically. Until today there has been no convincing proof that altering diet can lower the morbidity and mortality from CVD.

# Fat Burns in the Flame of Carbohydrate

I will try to demonstrate, by the use of diagrams and photographs, how the *excess of cortisol* and the overproduction of catecholamines impair carbohydrate metabolism and create conditions in which there is insufficient oxaloacetic acid for the oxidation of acetyl CoA, resulting in an increased plasma lipid concentration and increased cholesterol level. This is in full agreement with established biochemical principles, as shown by the following quotations: "*Cortisol excess raises blood lipids and the plasma cholesterol level.* This leads to arteriosclerosis" (Emphasis added. Keele and Neil 1982) — i.e., to CVD. *The nonoxidated acetyl CoA will be used for the biosynthesis of cholesterol,* as described by Keele and Neil (1961): "Cholesterol is synthesized from active acetate units in lieu of their conversion to fatty acids and leads to the rapid development of arteriosclerosis." These active acetate units are the acetyl CoA not oxidated by the Krebs cycle.

With my encouragement, one Danish university has been carrying out glucose tolerance tests and another measuring plasma lipid concentrations and cholesterol level in patients receiving testosterone therapy. Results show that pathological glucose tolerance is strikingly improved by testosterone (Fig.1). This clearly demonstrates a shift from anaerobic to aerobic metabolism, producing sufficient oxaloacetic acid for the oxidation of acetyl CoA, and at the same time enabling free fatty acids (FFA) to enter the Krebs cycle.

In Fig. 1, our attention is attracted by the way in which the creamy white opaque liquid containing triglycerides gradually becomes clearer and eventually transparent. This occurs concurrently with improvement in glucose tolerance and a decrease in cholesterol level. We must stress that these changes appear during — and because of — testosterone administration. Most important of all, the patient's circulation also improves. The claudication patient walks without difficulty, angina pectoris attacks slowly disappear, gangrene heals, and signs of hypoxia on the ECG are normalized. The processes are portrayed in the figure "in black and white" so that the reader can follow, with the naked eye, how testosterone administration shifts anaerobic metabolism to aerobic metabolism. Free fatty acids are conducted into the Krebs cycle, and carbohydrate metabolism is normalized — i.e., "fat burns in the flame of carbohydrate" — and the cholesterol level is decreased.

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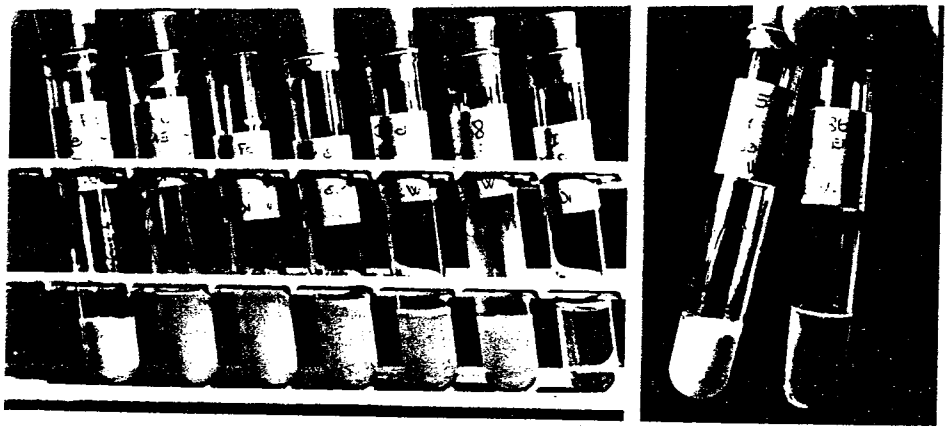

**Fig. 1 a.** The gradual clearing illustrates the gradual use of plasma lipids in the accelerated carbohydrate metabolism and the gradual transition from anaerobic to aerobic metabolism caused by testosterone treatment. **b.** The plasma before and after treatment.

# Free Fatty Acid Metabolism

Chylomicrons are cleared from plasma into fat depots by the action of the enzyme lipoprotein lipase (clearing factor), which is activated by testosterone (see, for instance, Breier et al. 1985). The intracellular hormone-sensitive lipase of adipose tissue catalyses the breakdown of stored triglycerides into glycerol and fatty acid with the latter entering the circulation. The hormone-sensitive lipase is activated by catecholamines and cortisol. (Despite the fact that only one of the enzymes is called "hormone sensitive," *both* lipases are, in my opinion, hormone sensitive.) Overproduction of catecholamines and cortisol leads to stimulation of the hormone sensitive lipase, raised acetyl CoA, impaired carbohydrate metabolism, and an increased level of cholesterol. Testosterone, on the other hand, activates lipoprotein lipase, leading the stream of triglycerides in the opposite direction, thereby reestablishing normal fatty acid metabolism, normal carbohydrate metabolism, and normal levels of cholesterol.

Many publications (e.g., Breier et al. 1985) confirm that there is a positive correlation between postheparin lipoprotein lipase activity and plasma testosterone, and a negative correlation between postheparin lipoprotein lipase activity and the extent of coronary artery disease.

The positive effect of testosterone on postheparin lipoprotein lipase, added to its effects on the other compounds of the cog-wheel system (see the section "The Nature of Cardiovascular Disease") further explains why we see the positive results of testosterone treatment of CVD.

In meetings with the late Sir Hans Krebs, we discussed the necessity of complementing the evidence for the clinical efficacy of testosterone therapy with an understanding of the biochemical processes involved. In 1982 (personal communication), he wrote:

> I feel that your clinical findings can stand by themselves and do not necessarily need underpinning as far as practical clinical medicine is concerned. After all, there are many methods of treatment which have no adequate biochemical foundation but are firmly based on clinical experience. I take it that you are anxious to see your clinical results and their interpretation underpinned by biochemical concepts, bearing in mind that all physiological and pathological events have some biochemical basis.

Integrating what we know about the linked roles of cholesterol, testosterone, cortisol, and the catecholamines shows broadly how the various pieces of the underlying biochemical jigsaw puzzle fall into place. More recent research is continually adding new details to the picture.

# The Nature of Cardiovascular Disease

In order to understand the role of cholesterol in CVD, it is necessary to describe the nature of the disease. Cardiovascular disorders are not diseases in the same sense as, for example, infections, which have a clear bacteriological etiology and can thus be treated and cured with antibiotics. *With CVD, the essential cause of the disease is within the organism itself.* It lies in the predominance of the influence of catabolism, represented by catecholamines and cortisol, over the role of anabolism, represented by testosterone and insulin, leading to an increase in cholesterol level.

Ageing brings with it an involution or impairment of many biological functions, resulting ultimately in the most final of involutions, namely death. In CVD, many of the same functions are also impaired; however, the impairment comes earlier in life and is more severe than in the case of the normal ageing process. For this reason, it is tempting to consider CVD as an acceleration of these ageing processes rather than as disease with a particular etiology. The idea is illustrated schematically in Fig. 2.

Since man appears to have a genetically determined lifespan, it is not possible to alter the downward course of line a, representing as it does the normal and irreversible deterioration of biological functions with age. Line b, on the other hand, represents reversible biochemical processes. Here, in contrast to the ageing process, it is possible to intervene through the use of an anabolic substance. As has become evident, the effect of this intervention is a decrease in the cholesterol level, an improvement in the oxygen supply to the tissues, an increase in fibrinolytic activity, an increased ATP level, an improvement of glucose tolerance, and a restoration of the negative nitrogen balance.

Line b represents the same situation as line a as far as the involution of biological functions is concerned, but the changes occur earlier in life, when the BMR is higher and there is more physical activity. This provokes CVD, since the oxygen requirement is still high at a time when its supply is being reduced. In contrast, as Keele and Neil (1982) write: "With advancing age, the basal metabolic rate (BMR) falls and the amount of physical activity declines." We could call this a teleological adaptation (though, of course, even with advancing age excess physical activity and stress will lead to CVD). It is worth noting that the female BMR is lower than the male BMR throughout life and that the muscle mass of a man is greater than that of a woman. In my experience, a man at the same age as a woman after menopause has virtually the same degree of muscle atrophy as the woman. The incidence of CVD among males is more than twice that among females before the "menopausal" age. After this age there is no difference between male and female incidence. On reflection, the sex difference in the BMR and muscle mass may to some extent help us to understand the higher incidence of CVD among men.

If this general view of CVD is accepted, it follows that the concept of a cure should be interpreted differently from that applicable to other diseases. In the case of CVD, cure means restoring a patient to the point on line a that would have been

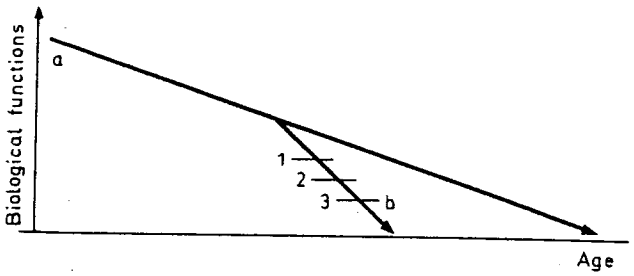


**Fig. 2.** Line *a* represents the normal age-dependent deterioration — due to antianabolic influences — of biological functions such as decreased stroke volume, cardiac output, oxygen supply, basal metabolic rate, glucose tolerance, insulin activity, and fibrinolytic activity, increased arterial tone and negative nitrogen balance. It is also apparent in increased catecholamine levels and pulse rate. (It is worth noting the influence of ageing on all complexes of the ECG which reach their highest amplitude between the ages of 15 and 25, after which they gradually decrease). Line *b* represents the *accelerated* deterioration of these functions in CVD patients. Three stages in disease development may be distinguished:

*1* Mild symptoms such as intermittent claudication, angina pectoris, and ECG changes on loading

*2* Claudication, pain at rest, angina pectoris, and ECG changes without loading

*3* Gangrene and infarction

Regarding line *a*, Keele and Neil (1982) write, "With advancing age the basal metabolic rate (BMR) falls and the amount of physical activity declines." Line *b* describes the same situation as far as the involution of biological functions is concerned, but the changes occur earlier in life when the BMR is higher and there is more physical activity. The result is manifest CVD.

Female BMR is lower than male BMR. This sex difference may contribute towards explaining the higher incidence of CVD in men.

occupied if he or she had remained in good health, subject only to the natural processes of ageing. Pushing a patient back *up* slope a is, of course, not possible.

This nuance of interpretation has important implications in dealing with CVD. It should not be taken as meaning that CVD is "incurable" in the accepted sense, or that the condition must be accepted without a fight. But CVD patients *treated with testosterone* often show such remarkable improvement that they are able to live the normal life which their age permits. Thousands of patients have been saved from amputation and premature death by testosterone administration.

Taking CVD in the lower limbs as a particular example, three stages of deterioration on line b can be distinguished: (1) intermittent claudication; (2) pain at rest; and (3) gangrene. If the patient at stage 1 can be helped to resume normal walking, then therapy has unquestionably been successful. But in view of the progressive character of CVD, arresting the development of the disease can also be regarded as a success. For instance, stabilizing for a considerable period of time the distance a patient can walk means that the condition does not deteriorate to stages 2 and 3. In addition, we must take into account the fact that everyone's circulation deteriorates as life progresses. For this reason alone, a patient's walking distance may not improve during treatment, and may indeed even become further restricted. It is also possible for someone to build up leg musculature without significantly improving the circulation in general. We must not forget that claudication is not a disease per se. In my experience, continued complaints about claudication can be accompanied by improvements on clinical measures, such as increased fibrinolytic activity, increased glucose tolerance, and decreased cholesterol level, that show the circulation *as a whole* has improved. One

must also pay attention to mortality as well as morbidity. Living longer with a shorter walking distance may suggest a better circulation than a short life with a longer walking distance. I have known many patients whose walking distance was improved but who were suddenly overtaken by a heart attack. The isolated improvement of walking distance may impose further strain on the heart and may in this way in fact provoke a heart attack.

Treating patients over a period of many years, I have been able to see that circulation deteriorates markedly as they grow older (line a), in spite of treatment. However, they kindly and thankfully remind me of their unhappy state when they first came to me, threatened with amputation, from which they were saved by testosterone. This makes me think of so-called serious scientists, and there are many of this sort, who want to conduct clinical trials over 10 or more years in order to evaluate treatment. It occurs to me that the layman seems to know the problem and the true nature of CVD better than they do, and takes into consideration the inevitable decline represented by line a, no matter what measures are taken or what treatment is given.

I will take as a specific example the case of a 55-year-old man whom I had been treating for between 4 and 5 years. I realized that this claudication patient had apparently not benefitted from long-term testosterone therapy. So I asked him whether he wished to continue. He insisted on this, even though his walking distance had not improved, and told me he knew several of my patients for whom the hospital had recommended amputation, but who had been saved from this step by testosterone. Some members of his own family had also been disabled by amputation. He therefore wished to carry on with treatment and was quite satisfied with the result. At least he still had both of his legs.

This ordinary workman revealed a whole chapter of medicine to me, after which I was able to draw Fig. 2 with the two sloping lines. Although several years older, biologically, than his own age group, his physical deterioration had been restored to a rate closer to that of normal ageing. In a two-group trial, this patient might have been wrongly included in the category of patients for whom treatment had been ineffective.

Let us consider what would have happened to this patient had he not undergone testosterone treatment. As described elsewhere in this book, all through life, circulation reflects a struggle between anabolic and catabolic forces, with the latter gradually gaining the upper hand and resulting in eventual destruction. The object of the struggle is that vital ingredient of life, protein. Catabolic forces are represented by catecholamines, under the permissive influence of cortisol, and decisive in the development of CVD is the dominance of these substances. The consequence is a shift towards anaerobic metabolism, resulting in cell necrosis, gangrene, and infarction. This could have been the result for this patient and for others with similar symptoms had they not been treated with testosterone.

Apart from these pathological effects, catabolism has, of course, a normal physiological role in the life process — through its involvement in physical activity, organ functioning, heat production, and blood glucose regulation. Concerning the pathological effects, I refer to Keele and Neil (1982): "Cortisol promotes catabolism of proteins. Normally this breakdown of protein is counterbalanced by anabolic processes but excess of cortisol causes a negative nitrogen balance." This impairs all the other biological functions that lead to CVD, decreasing insulin and dehydrogenase activity, decreasing fibrinolysis, *increasing the cholesterol level*, impairing carbohydrate metabolism, and decreas-

ing pH and ATP production. These destructive processes are interlocked, like a series of cogwheels, so that when one wheel moves the others follow. We must therefore counteract the negative nitrogen balance by the administration of anabolic steroids if the organism itself is not able to restore a normal homeostasis. The other factors represented as cogwheels will then also turn in a positive direction.

My book rests on certain fundamental thoughts which parallel those found, for instance, in *Samson Wright's Applied Physiology* (Keele and Neil 1961). "In the past, the detailed information that has accumulated about the minute structure of the cell was regarded as mainly of academic interest; it is now becoming evident that the findings of cytology are of outstanding significance to both physiology and pathology and hence to practical medicine." It is clear that these cytological findings are also essential to my approach to the problems dealt with in this book. The *Samson Wright* quotation continues, "The other main branch of physiology deals with the *co-ordination* of the individual parts of the organism to form an efficiently-functioning whole; how it is, for example, that the 'whole is greater than the sum of its parts'; and how it is that the parts behave as if they 'knew' of the existence of the whole which they subserve ('a whole presupposed of its parts'). This aspect of physiology is generally considered under such headings as organization, regulation, or integration." This is in fact the essence of my cogwheel theory. It confirms that there is no sense in being engaged with one physiological "part" out of the "whole" while not considering the other "parts." Failure to realize this led for example to the unfortunate experience with clofibrate, when this substance was used (quite unscientifically) specifically to lower the cholesterol level, without reference to other, related processes.

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## Difficulty in Distinguishing Ageing and Pathological Processes

Those wishing to probe more deeply into the whole phenomenon of CVD must take account of the theory that the biological functions that decline gradually with age (line a in Fig. 2) are essentially the same as those that decline more suddenly in disease (line b). For this reason, as Keele and Neil write (1982, p 528), "It is often difficult to say whether degenerative changes are *physiological or pathological* in nature, but predisposition to fatal infections, malignant disease and *cardiovascular catastrophes* account for the vast majority of deaths in old people." (Emphasis added)

With particular reference to the cardiovascular system, Goldstein (1978) comments: "It has so far not proved possible to distinguish the age-related and generally established 'physiological sclerosis' with certainty from pathological arteriosclerosis." From the broader perspective, Doyle (1983) refers to the close connections between the general process of ageing and pathology:

> Man, like other biological species, appears to have a genetically determined lifespan. That is to say, those individuals who escape accidental early death due to trauma or infection survive for a finite period of time, which has not altered appreciably since historical records have been available. The word "age" is often used to denote the passage of time which refers to chronological age. The ageing process, however, involves other factors than time alone, such as physical and mental illness, trauma and stress, which accelerate the normal ageing process. Ageing therefore involves two main processes: time-related, involutional "physiological" changes and disease or stress-induced "pathological" changes. *In practice it is often difficult to dissociate these two processes.* (Emphasis added)

On this point, see also the section "The Negative Nitrogen Balance" which comments on an article by Sobel and Marmorston.

With regard to line a, Doyle (1983) comments further:

> The effects of ageing on the cardiovascular system include a reduction in cardiac output, an increase in energy expenditure for given amounts of cardiac work, increased oxygen debt and an increase in peripheral vascular resistance. These anatomical and physiological changes lead to impaired tissue perfusion and nutrition adding to or accelerating the time-related changes at organ level.

Two further examples of processes that occur naturally with age, but which are also found in CVD, are given by Franke (1981). First, he cites impaired carbohydrate metabolism and associated reduced glucose tolerance, which arise from decreased insulin activity. Secondly, Franke describes what he regards as the fundamental change affecting the heart and circulatory system, namely the general decline in its ability to adapt to physical exertion (see also Starnes 1981). Franke writes, "The stroke volume and maximal oxygen uptake — which provide a measure of the physical reserve — all decline after the thirtieth year of life" For instance, the amplitude of all complexes on the ECG decline after 25-30 years of age.

It is relevant here to recount some investigations I have carried out in two groups of men, one a group of patients about to begin a course of testosterone

treatment and the other a group of apparently healthy men of the same age who were about to start physical training. I had the opportunity to arrange such a trial since I had opened a clinic for elderly people where I could offer free testing or treatment.

I was not surprised to find that my laboratory tests showed virtually no difference between the two groups. Both had similar degrees of impaired carbohydrate metabolism and ECG abnormalities. Yet the former group considered themselves to have CVD while the latter did not. Presumably, the reason is that my patients, who were about to receive testosterone, were still leading active lives and had experienced pain, for instance in the form of claudication or angina pectoris. The members of the other group, having retired completely from any active work, were able to take life more easily, conscious or unconscious of the fact that they were unable to perform the same physical and psychological tasks as previously. They had probably accepted this situation, thereby avoiding the symptoms experienced by the active members of the first group, and consequently did not consider themselves to be suffering from CVD; neither did their own doctors.

The trial confirmed that it is very difficult to say whether degenerative changes are physiological or pathological. Nevertheless, one group considered themselves ill and demanded treatment in keeping with the results of the laboratory tests. As a doctor I could not deny them this treatment since we know that it is not possible to distinguish clearly between physiological and pathological changes.

Another example of a variable which occurs both in CVD and in the ageing processes is given by Raab (1949) when he describes a fourfold increase in the catecholamine concentration in the heart from youth to old age. The *Handbook of Physiology* (Klensch 1966) also shows that venous noradrenaline levels, for example, rise gradually by 30% between early adulthood and retirement age (Table 1).

**Table 1.** Age related to venous plasma norepinephrine levels in man (adapted from Klensch 1966).

| Age | Plasma norepinephrine (ng/ml) |
|---|---|
| 20-29 | 0.266 |
| 60-68 | 0.350 |

The gradual transition from youth to old age can be seen in daily life by watching the way in which people of different ages perform simple, everyday activities such as climbing stairs. A young boy ascends at great speed, like a rocket, assured in the knowledge that his powerful cardiac "engine" will maintain his momentum until he reaches the top. The adult does not have the same ability as the young boy and must evaluate the situation accordingly. The retiree knows that he cannot sprint as he did in his youth and so, consciously or unconsciously, adjusts his tempo to suit the occasion. If he exerts himself beyond his limit, the result is dyspnea and hypoxia with increased pulse rate, which in his case is more risky and may be fatal, as his lower BMR is adjusted to a reduced amount of physical activity. Ganong writes (1975, p 464): "The maximal heart rate achieved during exercise decreases with age. In children, it rises to 200 or more beats per minute; in adults, it rarely exceeds 195 beats per minute, and in elderly individuals the rise is even less."

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Circulation becomes less effective as soon as one grows out of childhood. This has been well demonstrated by athletes who attempted to copy the movements of active playing children exactly — and had to give up. Even the fittest athletes accept that as they grow older they must give way to younger sportsmen. It has been reported that an 11-year-old child weighs on average 42 kg and has a heart volume of 442 cc. The 16-year-old weighs 72 kg but has a heart volume only 100 cc greater than the child. For the older adult, the heart is like an engine of lower power, driving a car that is far heavier. It is, after all, the strength and capacity of the heart that is the decisive factor in the circulation. This strength and capacity decline with age.

# pH as a Variable in Metabolsim

In CVD, metabolism is anaerobic and the catecholamine level is raised. As Table 2 shows, high catecholamine levels are associated with an increased risk of death during myocardial infarction.

**Table 2** Plasma catecholamines in myocardial infarction (adapted from Griffiths and Leung 1971)

| Mortality (n) | Plasma catecholamines (ng/ml) | |
|---|---|---|
| | Epinephrine | Norepinephrine |
| 7 of 9 | 0.27 | 4.1 |
| 2 of 8 | 0.12 | 1.5 |
| 1 of 8 | 0.09 | 0.61 |

The potential adverse effects of catecholamines on the circulatory system are also well demonstrated in patients with pheochromocytoma. Overproduction of catecholamines leads to CVD symptoms, including angina pectoris, hyperglycemia, and glucosuria. These symptoms disappear once the tumor is removed (Raab 1949).

The relationship between high catecholamine output and low pH is well established (a feature of anaerobic metabolism; see Table 3).

**Table 3** The influence of pH on catecholamine output of dog adrenal gland perfused with blood (adapted from Nahas et al. 1967).

| pH | Total catecholamine output (ng/gland per min) |
|---|---|
| 7.41 | 70 |
| 6.84 | 532 |

Testosterone shifts the metabolism from anaerobic (with its accompanying high cholesterol level) to aerobic states, improving the range of adverse features associated with anaerobic metabolism, including low pH. It is essential for normal metabolism that the body pH remains within a narrow range. Green (1976, p 92) writes in relation to enzymes: "The enzymes of the body are proteins, and it is because their activity depends on their ionization that body pH must be kept at exactly the correct level." Normal aerobic metabolism depends on normal enzyme activity.

# Stress

CVD has been associated with stress, which can be divided into two forms: eustress and dysstress. "Eu-stress" is the level of stress which causes a sympathetic response (in connection with "permissive" cortisol), leading to rebound parasympathetic activity. In daily life, the state is achieved when suitable, sensible physical activity is followed by relaxation and recuperation. Mental and physical exercise beyond the point of eustress becomes dysstress, where the sympathetic state dominates the parasympathetic, causing damage to the circulation. Let us emphasize that eustress has been proved to increase testosterone production and decrease cholesterol levels; and dysstress the reverse. Eustress occurs in normal metabolism and may deplete the glycogen depots. Cortisol promotes gluconeogenesis partly by favoring the release of amino acids from protein and partly by inducing the synthesis of gluconeogenic enzymes in the liver — necessary to maintain normal glucose level. Dysstress means excess of cortisol and catecholamines, leading to hyperglycaemia and impaired carbohydrate metabolism, i.e., CVD.

The combined effect of catecholamines and cortisol is to ensure a sufficient supply of fuels for "fight or flight" by greatly increasing the amount of fatty acid and glucose which is available. Unfortunately, this early evolutionary adaptation is largely irrelevant to the mental stress most commonly encountered in today's civilized society. Blood glucose and fatty acid levels are raised by the hormone sensitive lipase, without being followed by corresponding physical activity. (This situation has been likened to accelerating your car to top speed while at the same time keeping your foot firmly on the brake.) The fuels made available are not converted into energy by turnover in the Krebs cycle, and, as I have suggested, the surplus of acetyl CoA results in an *increased cholesterol level*. We know that physical activity (eustress) can increase the production of testosterone, which improves the activity of postheparin lipoprotein lipase counteracting the effect of the hormone sensitive lipase.

# Infarction Due to Metabolic Processes Other than Vessel Occlusion

Like other cells, the cells in the arterial wall and myocardium are subject to changes in metabolism. We know from embryology that in the early stages of development the vascular system consists of a series of vessels in which the blood is kept circulating by the rhythmical contraction of their walls. After a short time, parts of the vessels undergo changes which result in the formation of the heart. Once the heart is established, the continued circulation of blood depends on the regular contraction of the muscular substance of its walls. This common origin underlies the possibility that lesions of the arterial wall and infarction have the same cause. Indeed, it would be unscientific to suggest that anaerobic metabolism has an effect on certain cells but not on others.

This view is strongly argued by Zemplenyi (1968):

> The arterial wall is a metabolically active living organ that has its own equipment for the numerous anabolic and catabolic processes that are fundamental to all living matter and vital for synthesizing normal and abnormal tissue-components....
> Decreased Krebs cycle enzyme activity is a hallmark of that form of protracted vascular damage that appears to prepare the ground for the development of atherosclerotic lesions in mammalian and avian arteries.

Concerning arteriosclerotic lesions I refer to Anderson and Scotti (1976). The injured vessel wall releases ADP which facilitates platelet aggregation. The administration of testosterone favorably affects the activity of enzymes in the Krebs cycle, which increases the level of ATP relative to ADP, thereby inhibiting platelet aggregation (which is in conformity with the WHO Madrid report 1972). Concerning the decrease in activity of Krebs cycle enzymes accompanying anaerobic metabolism, Janda et al. (1976) write: "Administration of 19-nortestosterone propionate prevented enzymatic changes which are typical for chronic ischaemia, primarily the decrease in the activities of dehydrogenases of Krebs cycle tricarboxylic acids (MDH and SDH)."

The effect of testosterone on enzyme activity in patients suffering from CVD is being investigated at the Institute for Biology and Chemistry at Roskilde University Center, Denmark. Preliminary reports (that agree with the article just quoted) show improved activity of succinate dehydrogenase (SDH) and glucose 6-phosphate dehydrogenase as well as a decreased cholesterol level. Kowalewski (1963) examined the activities of mitochondrial respiratory enzymes in the liver of normal rats and of rats treated with cortisone and/or the anabolic steroid methandrostenolone: "The activities of malic dehydrogenase and DPN-cytochrome-c-reductase were decreased in cortisone treated rats. This depression was reversible and interruption of treatment resulted in normalization of activities of both enzymes. Simultaneous treatment of rats by cortisone and the anabolizer did not, however, prevent this depression. *The activities of both enzymes were increased in rats treated with methandrostenolone.*"

Zemplenyi emphasizes that the cells of the arterial wall depend on an adequate oxygen supply. The result of an unsatisfactory oxygen supply is a shift towards anaerobic metabolism (see in this connection Okamoto 1983, discussed below).

The two factors mentioned by Zemplenyi, i.e., Krebs cycle enzyme activity and lack of oxygen, are factors proved to be controlled by testosterone.

Agreeing with Zemplenyi, Boyd (1965) writes, "These vessels (arteries) are not mere passive tubes. The electron microscope has revealed a metabolic machinery capable of great activity, which burns sugar, consumes oxygen and liberates carbon dioxide, in addition to synthesising *cholesterol*, mucopolysaccharides and proteins." As a matter of fact Boyd, having witnessed the results of testosterone treatment during a visit to my clinic, wrote in his book *Pathology for the Physician* (1965): "I have personally seen in Copenhagen a remarkable demonstration of the relief afforded by these measures, in some cases saving the patient from amputation and even suicide. (Jens Møller, personal communication)."

In this regard it is appropriate to refer in detail to work by Raab, who says that in more than 50% of myocardial infarctions the cause is not occlusion of an artery but a direct effect on the myocardial cell. He stresses that metabolic explanations may be sought at the cytological level.

> Regardless of the variously reported non-existence of thrombi and vascular occlusions in up to more than 50 percent of myocardial so-called infarctions, and regardless of frequent gross discrepancies between the incidence, degree and location of coronary vascular vs myocardial structural lesions, such terms as "coronary occlusion", "coronary thrombosis", "coronary atherosclerosis", "coronary heart disease", "coronary artery disease", or plainly "a coronary" are indiscriminately and interchangeably used in clinical practice and textbooks, and especially in epidemiological reports....
> Profound, potentially pathogenic, and mutually aggravating influences of sympatho-adrenal catecholamines and of adrenal corticoids upon the oxygen economy and electrolyte balance of the heart muscle have been intensively investigated over many years. This popular but somewhat worn out cliche for "coronary heart disease" may more appropriately be read as meaning "cardiac hypoxic dysionism" in keeping with present day knowledge and concepts. (Raab 1972 a)

I agree that the different names for this disease are very confusing. This confusion is complete when it is claimed that such names are justified because they describe the nature of the pathogenesis of CVD. I use the term "cardiovascular disease" to mean changes in the heart itself or in the heart and in the arteries.

Raab described the situation in the following way in 1969:

> For 50 years, a mechanistic interpretation of hypoxic degenerative heart disease prevailed as being merely a problem of vascular oxygen supply to the heart muscle. Hardly any attention was paid to the fact that vital oxygen availability to the myocardial tissue depends not only on vascular oxygen supply but also on metabolic oxygen consumption by the myocardial tissue. Any major discrepancy between these two logically inseparable factors is bound to create local hypoxia and to result in functional and structural alterations that are, in turn, largely mediated by derangements in the cellular electrolyte balance.

Raab here draws attention to the fact that infarction is not merely a problem of vascular oxygen supply to the heart muscle but also a problem of metabolic oxygen consumption by the myocardial tissue. In a later work (1972 b), he continued:

> Today's literature suggests that, jointly with vascular oxygen-supply-limiting factors, centrally controlled neuroendocrine mechanisms dominate the myocardial pathogenesis. By interfering with myocardial oxygen economy (catecholamines) and carbohydrate metabolism (glucocorticoids), they derange vital myocardial electrolyte equilibrium (loss of potassium and magnesium, gain in sodium), thus disturbing stimulus formation and conduction, cell contractility and structure, largely under the influence of civilization-induced emotional and environmental stresses.

In this abstract, Raab underlines exactly the same processes as I do: namely how catecholamines interfere with the oxygen economy, and cortisol with carbohydrate metabolism. The way in which excess cortisol and the overproduction of catecholamines lead to an *increased cholesterol level* is well documented in this book. Raab's ideas coincide very well with the views that I hold and they offer a broader explanation of the pathological changes seen in CVD.

The theory that the origin of atherosclerosis is the same as that of infarction and gangrene can be widely supported. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, for example, Weiner (1980, p 150) writes: "Large or repeated doses of epinephrine or other sympathomimetic amines given to experimental animals lead to damage to arterial walls and myocardium, so severe as to cause the appearance of necrotic areas, indistinguishable in the heart from myocardial infarcts." This agrees with the view that the overproduction of catecholamines (with the "permissive" influence of cortisol) is a pathogenic factor in CVD. Circulating catecholamines, which derange the metabolism of the arterial wall, and the injured vessel wall itself, by releasing ADP, promote thrombosis (Anderson and Scotti 1976; Keele and Neil 1982).

The consequences of inhaling low levels of oxygen throw further light on the problem. Okamoto et al. (1983) make some interesting comments on the results of reducing oxygen tension in inspired air. They studied "the effect of hyperoxic or hypoxic inhalation on blood lipid levels and the development of atherosclerosis in young male WHHL rabbits" and describe their experiment as follows:

> They [the rabbits] were exposed to ordinary room air containing different concentrations of oxygen: 6 animals were exposed to 40% oxygen (hyperoxia group) or 5%-10% oxygen (hypoxia group) for 5 h a day, 5 days a week for 8 weeks. Four control rabbits inhaled ordinary room air. The following results were obtained: the severity of aortic lesions significantly decreased in the hyperoxia group; plasma triglyceride levels were elevated only in the hypoxia group. Likewise, Adams and Zemplenyi found that hypoxia in aortic tissue resulted in impairment of several energy-linked enzyme activities and related this to the development of atherosclerotic changes. Thus, inhalation of low levels of oxygen may, at least in part, locally influence the process of atheroma formation in aortic tissue through alterations in tissue lipid catabolism. High oxygen inhalation may reverse the process.

Here again we see that anaerobic metabolism can lead directly to changes in the blood vessel wall.

David Short wrote in an article entitled "The Great Circulatory Paradox" (1977) that:

> *An appreciation of the role of factors other than atheroma in the aetiology of infarction is essential for rational prevention and treatment....* First there is the claim that in many cases of myocardial infarction the thrombus is younger than the infarct and therefore *a consequence rather than a cause of it*. This claim received strong support from a study in which fibrinogen labelled with radioactive iodine was injected into patients shortly after the onset of pain of myocardial infarction and the coronary arteries examined for radioactivity in those who died. In many of the cases studied, the occlusive thrombus was found to be radioactive, suggesting that the thrombus was laid down after the onset of infarction (on this point see also Ehrlich and Shinohara 1964)... Coronary atherosclerosis is very common in adult life, and the severest degrees are often seen in people without any history of cardiac disability or evidence of either old or recent myocardial infarction.... Experimentally, myocardial infarction has been reported after excessive exercise in untrained animals with healthy coronary arteries. Clinically, it is by no means rare for myocardial infarction to be precipitated by an outburst of *intense anger* or severe exertion, especially if this is sudden and relentless. (Emphasis added)

Short thus supports the same idea: it is not necessary for a myocardial infarction to be preceded by arterial occlusion. The fact that it may occur during severe exertion indicates that competent control of physical training is a prerequisite for improving deteriorated circulation.

Selye (1969) provides another report of this fact:

> Unlike the common myocardial infarcts described in textbooks, those elicited in animals after pretreatment with corticoids and sodium salts are not accompanied by vascular occlusion. It is clear that animal myocardial necroses can be produced without coronary obstruction, apparently as a consequence of a direct interference within the cardiac muscle itself. It is also evident that these necroses can be prevented by chemical agents [see Gudbjarnason 1972] which act on the myocardium directly and not through improvement of its blood supply.

Selye makes it clear that myocardial necroses can be produced by administration of corticoids without coronary obstruction. I agree this is so, and argue further that these necroses can be prevented by a chemical agent — namely testosterone — which has the effect of counteracting cortisol. (The theories of Sobel and Marmorston, presented later, accord with those of Selye. See also Kowalewski 1963, which underlines the necessity of using testosterone to counter the effect of cortisol.)

*To sum up: we must not consider arterial walls to be inert pipes, and the medical problem of CVD cannot be satisfactorily solved by replacing the arteries with plastic tubes.* This form of surgery is purely symptomatic. I am sure any doctor feels unhappy when compelled to give symptomatic treatment to a suffering patient, instead of getting to the root of the disease and acting accordingly.

# Testosterone as an Alternative to Surgery for CVD

Since the establishment of my clinic in Copenhagen, scientists of the highest reputation have supported my view that CVD is not a surgical but a medical problem. This does not imply that surgery has not helped some CVD patients, but where this has been so — in my experience — it is only for a very limited period of time. I believe surgery involves such great risks during and after the operation, and is frequently followed so quickly by amputation, that a medical alternative ought first to be presented to the patient. Another point is that postsurgical patients are treated with an anticoagulant, which is unphysiological, risky, and potentially fatal. On the other hand, medical treatment with a physiological substance, like testosterone, is not accompanied by any risk.

Some of the drawbacks of coronary bypass operations have been pointed out by Atkinson (1983), who writes: "Atherosclerosis progresses more rapidly in bypass grafts than it does in native coronary arteries. It may take a person 50 years to build up enough atherosclerotic plaque to clog his coronary arteries, whereas it may take only three or four years to clog his bypass grafts." Further, Atkinson found that in many patients, "total occlusion of the graft occured soon after surgery." The majority of patients died from heart disease. Atkinson concluded, "We don't know if their deaths were related to changes seen in their bypass grafts, or because of atherosclerosis in their native coronary arteries."

It was pointed out at the EOCCD symposium in Munich (1985) that patients about to have bypass surgery often have the kind of pathological changes in ECG which have been shown to be improved by the administration of testosterone. It is therefore only natural to ask why testosterone is not tried before submitting the patient to the risks of angiography and operation.

## Peripheral Vascular Disease

We know that the endothelium of the arteries and the blood corpuscles form a unit, since they have exactly the same embryological origin. The peripheral angioblasts become endothelial cells and those more centrally situated are the ancestors of all the blood corpuscles. This unity is one obstacle to the replacement of part of the vascular system by inert plastic pipes. The blood cannot be expected to react in the normal, optimal, physiological way, having lost its natural intimacy with the arterial wall. By "natural intimacy" I mean the relation between the metabolism of the arterial wall and the metabolism of, for example, the platelets. This is important since we know that sufficient ATP production in the injured vessel wall is decisive for inhibiting platelet aggregation (see Keele and Neil 1982, p 30).

I could forgive a layman for suggesting that a worn out artery be replaced with a brand new plastic pipe, transporting blood like ordinary water; but I am amazed

when physicians, despite their scientific background, can proceed in such a way. I am left almost speechless that they do not try hormone treatment, the positive results of which were known long before I entered the arena.

Another major objection to treating blood vessels like plumbers' pipes is that the entire vasculature is under the control of the autonomic nervous system, which — in conjunction with osmoregulation and volume regulation — ensures the homeostasis of the circulation. Inert plastic pipes do not participate in this absolutely essential system of regulation. By not using the fibrinolytic agent testosterone, recommended by the WHO, one excludes the possibility of helping the patient without a risky operation. Indeed, the possibility of establishing a natural regulation is eliminated at the very point where it is of greatest physiological importance.

# Diabetic States and CVD

Insights gained from a study of the role of anaerobic metabolism in CVD are applicable to other disorders, among them diabetic states. Patients with insulin-dependent, juvenile-onset diabetes can oxidize ketone bodies, built up from acetic acid units. This is an attempt to provide an alternative, noncarbohydrate energy source. If ketone-body production exceeds the rate at which dissimilation can be carried out by the tissues, then ketone bodies accumulate in the blood (ketosis).

Unlike juvenile-onset diabetics, maturity-onset diabetics do not produce any more ketone bodies than a normoglycemic person (Ganong 1975, p 265). Prevented from entering the citric acid cycle by impaired carbohydrate metabolism and the resulting lack of oxaloacetic acid, the acetic acid units synthesize cholesterol instead of ketone bodies.

The "diabetic" state of CVD patients, which can be verified by glucose loading and is perhaps present more generally, has been diagnosed as maturity-onset diabetes. However, I am not confident that this diagnosis is correct; I am more inclined to consider the abnormal glucose metabolism of these patients as a sign of deterioration in circulation.

I have demonstrated normalization of impaired carbohydrate metabolism and a *decrease in plasma cholesterol* following administration of the physiological agent, testosterone. This substance, and not oral antidiabetic agents, is the appropriate treatment for such cases. Figures 1a and b vividly demonstrate that clear improvement in so-called maturity-onset diabetes can be achieved without the use of nonphysiological antidiabetics. The test tubes clearly reveal impaired carbohydrate metabolism and increased plasma FFA at the start, and their normalization by testosterone.

Others are also suspicious of oral hypoglycemic drugs. The *Goodman and Gilman* textbook itself leaves no doubt about its position. Its verdict (Larner 1980, p 1513-14) is:

> The sulfonylureas should be used only in patients with diabetes of the insulin independent type who cannot be treated with diet alone and who are unwilling or unable to take insulin if weight reduction and dietary control fail. The physician must realize that he is most likely using these agents only to control symptoms associated with hyperglycaemia, and that dietary control with or without insulin is more effective for this purpose. There is no evidence that the oral hypoglycaemic agents prevent cardiovascular complications from diabetes, and the best data available, even though controversial, suggest that the incidence of such complications may be increased in patients taking these drugs. This risk is too high a price for the convenience of an oral agent, unless ALL other measures have been exhausted.

Only too often I have seen the high price patients have to pay in the form of gangrene when they have been treated with oral hypoglycemic agents.

Before any use is made of unphysiological antidiabetic agents, serious attempts must be made to avoid the complications mentioned in *Goodman and Gilman.* With complex, interacting life processes, it is altogether wrong to concentrate on one variable to the exclusion of others.

In a state of maturity-onset diabetes testosterone administration has a protein-sparing effect, diverting amino acids from glycogen to protein synthesis, and so

benefits carbohydrate metabolism. Testosterone changes the nitrogen balance from negative to positive, and also increases dehydrogenase activity in the Krebs cycle, restoring the balance between aerobic metabolism and catecholamine production along with its effect on glycogen breakdown. I explain the pathogenesis of maturity-onset diabetes as a state with a lack of oxygen, and I have demonstrated how testosterone can counteract this state.

It is quite another situation when we come to juvenile-onset diabetes, where insulin is used in treatment. In this case it appears to be difficult, if not impossible, to give an exact explanation of the pathogenesis, as I have done in the case of maturity-onset diabetes caused by anaerobic metabolism. As far as treatment is concerned, we must admit that the biological effects of insulin are so far-reaching and complex that the only way of trying to understand them is by looking at the consequences of insulin deficiency, produced in experimental animals by pancreatectomy or by destruction of $\beta$-cells with the drug alloxan.

Juvenile- and maturity-onset diabetes have quite different symptoms. The juvenile type is characterized by polyuria, polydipsia, weight loss in spite of polyphagia, and ketosis. Only in special cases does anaerobic metabolism occur. This is therefore not the etiology, as it is in the maturity-onset disease.

As mentioned above, the two types of diabetic states should be treated differently: pancreatic (juvenile-onset) diabetes with insulin every day; and steroid (maturity-onset) diabetes with testosterone. *In both cases the aim is to normalize the blood glucose level.* When the dosage is determined and the exact effect on the glucose parameter evident, other relevant parameters will be normalized with both forms of treatment.

In the case of pancreatic diabetes it is generally accepted that you need no further investigations such as dividing patients into two groups for a placebo control trial. Why then is it considered necessary to demand placebo control trials in the case of CVD, which is *similar* to maturity-onset diabetes?

May I repeat what I have said in another context. It would be extremely difficult to persuade me as a member of the medical profession to take a group of 20 patients suffering, for instance, from gangrene and claudication, and divide them into two groups, treating the people in one group but not in the other so that a comparison could be made. I do not wish to treat my patients and fellow human beings as if they were rats. Should a patient on physiological saline die from cardiac infarction or cerebral haemorrhage during such clinical trials, I could not continue to serve as a doctor. Having refrained from correctly treating the patient with hormones, I would consider myself to some extent guilty of his death and would actually have acted illegally. Imagine also that a gangrene patient were to be given salt water instead of a medical treatment which is known to have helped thousands of others. Even if an amputation did not prove fatal, he would be disabled for the rest of his life. What would such a patient think and feel about doctors who allowed his disastrous condition to remain untreated and so ruined his life?

Initially, I treat my so-called "maturity-onset diabetic" patients with relatively high doses of testosterone to gain an immediate effect. The dosage is reduced gradually and I usually end up by giving testosterone depot 250 mg once a month. It is accepted in medical centers that maturity-onset diabetes is often found in patients with CVD — but it is especially pointed out that ketone bodies are rarely found. This makes it seem as if two different diseases — diabetic and cardiovascular — are being dealt with. But this is not the case. It has already been

established that impaired carbohydrate metabolism is an important *complicatior* of CVD, and not a separate disorder. Simple blood and urine tests alone often suffice to reveal a diabetic state, which can be further confirmed by an oral glucose test (Fig. 3). It is with this type of patient that the diagnosis of maturity-onset diabetes is most frequently used.

Elsewhere, such patients are treated with hypoglycemic agents. The doctor does not notice that the real problem is CVD, and the patient's circulation worsens as a result of treatment as described in *Goodman and Gilman*. In my hands, these patients receive testosterone, both for their diabetic state and their CVD — as a rule with good results (Fig. 3). Their improvement is reflected in a fall in *cholesterol level*, increased fibrinolytic activity, increased pH, increased 2,3 DPG, increased activity of enzymes in the Krebs cycle, and a reduction in signs of hypoxia in the ECG. I repeat: to proceed in a scientific way, all the disorders developing from anaerobic metabolism have to be tackled together. Concentrating on one irregularity alone is a serious mistake.

The pharmaceutical index, based on established research and authorized and edited by the Association of Danish Doctors, itself indicates anabolic steroids for vascular diseases. More significant still, the index states that laboratory analyses following use of testosterone show decreased serum triglycerides, increased fibrinolysis, increased plasma proteins, and a *lowering of blood glucose*. This again demonstrates (and indeed officially recognizes) the connection between CVD and impaired carbohydrate metabolism. It should only be a short step from the recognition that testosterone has the effect of lowering blood glucose to recognition of the value of testosterone therapy in the treatment of maturity-onset diabetes.

Evidence of the relevance of testosterone therapy for maturity-onset diabetes continues to accumulate. For example, the *testosterone level was found to correlate negatively with blood glucose among both coronary heart disease patients and normal controls* studied by Phillips et al. (1983).

Wagner et al. (1975) mention disturbances of carbohydrate metabolism and lipid metabolism in atherosclerosis. They investigated patients with myocardial infarction and found that they showed significantly *higher* blood sugar and significantly *lower* serum testosterone concentrations. *Furthermore, they showed significantly higher serum levels of total lipids, total cholesterol, and triglycerides.*

Certain additional comments are appropriate to end this chapter. I have always wondered why Eskimos are used in research on metabolism in connection with the cholesterol problem since we know that "Eskimos can tolerate high fat diets that would cause gross ketosis in the average European" (Keele and Neil 1982, p 462). Again I am left speechless; how can anybody undertake CVD research on Eskimos without taking the above into consideration? Ketone bodies and cholesterol are both synthesized from acetate units. We know that the circulation is very dependant on hormone production, and here again we know that Eskimo women cease to ovulate during the long winter night and the regular menstrual cycles and sexual vigour return in the spring.

To make another slight digression, the situation in regard to oral hypoglycemics reminds me of the time scientists became hypnotized by plasma cholesterol and used clofibrate to decrease its level, with fatal results similar to sympathectomy. Again, a symptom was being attacked without reference to its cause. I also warn against being mesmerized by hypertension (and other indications of a deteriorated vascular system) into indiscriminate distribution of antihypertensive

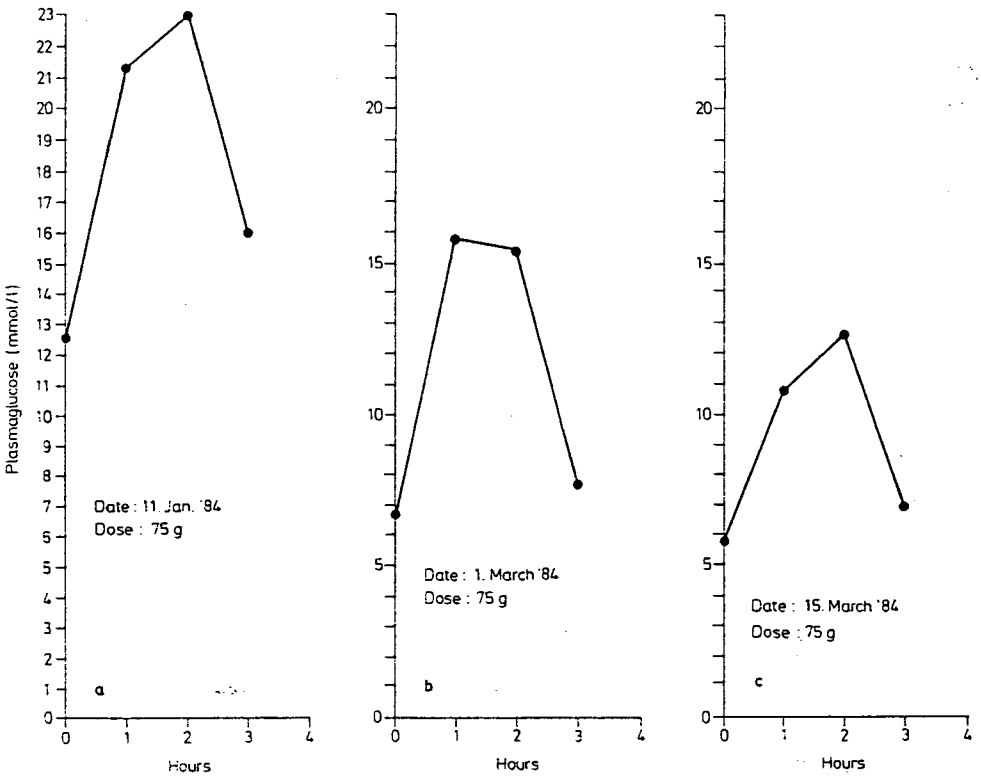


**Fig. 3.** Illustrates three glucose tolerance tests. The first (a) made before treatment, the two others (b and c) made during treatment with testosterone 250mg three times a week.
Note that the third curve (c) demonstrates a normalization of the glucose tolerance.

drugs. As I have said, it is risky to interfere with the autonomic nervous system either medically or surgically. I have witnessed tragic results of sympathectomy with cases ending in gangrene and death. Male patients have had their lives ruined, suffering from impotence and lack of erection and a fatal deterioration in their circulation. Normalized testosterone production parallels a normal circulation.

Looking at the animal kingdom, it is clear that a sympathectomized animal could not fend for itself and, in the struggle for existence, would soon succumb to the hazards of the environment. I cannot imagine how CVD specialists, who should have a scientific background, do not realize that it is unjustified to interfere in the way they do, paralysing one part of the nervous system without taking into account the malfunction that will be caused in the complementary parasympathetic part.

The production of ketone bodies in cases of CVD is not different from that in healthy people. This is presumably an adaptive measure. Because lack of oxygen is a feature of CVD, ketone bodies cannot be oxidized to energy, as they are in juvenile-onset diabetes. In CVD acetyl CoA is, therefore, used for the synthesis of cholesterol instead of ketone production. I have never seen a description of a pathological state of ketoacidosis leading to diabetic coma in these patients. Furthermore, I have to give high doses of testosterone to some patients for a short period of time, and in these cases the patients may experience symptoms resembling insulin shock. I advise these patients to carry glucose tablets in case of hypoglycemia just as juvenile-onset diabetic patients do.

It is a well-known fact that CVD patients show a reduced glucose tolerance. Fuller et al. (1980) showed that CVD mortality rates are twice as high in patients with reduced glucose tolerance. The same relationship has been found in many other investigations.

On the declining path represented by line a in Fig. 2 we find increasing impairment of both carbohydrate metabolism and the circulation. This fits in well with my theory that maturity-onset diabetes is a sign of CVD and impaired carbohydrate metabolism.

# Use of Anabolic Steroids in Surgical Stress

Sympathetic dominance of the autonomic nervous system under the influence of "permissive" cortisol is a physiological reaction commonly seen in response to stress, which can be either mental or physical in character. To shed further light on the metabolic changes which occur in response to sympathetic dominance, the effect of surgery can be taken as an example.

An operation is accompanied by metabolic and endocrine changes which are proportional to the duration and seriousness of the surgery. Physiological responses include an increase in plasma cortisol, catecholamines, cholesterol level, and triglycerides, a negative nitrogen balance, and a decrease in testosterone. In other words, there is a shift from aerobic to anaerobic metabolism, or more precisely, a shift from ATP to ADP — hence the risk of thrombosis. Oyama et al. (1972) measured testosterone levels in 14 male patients. The lowest concentrations were found on the first postoperative day, but plasma testosterone levels remained significantly depressed for a week. Damber and Janson (1978) investigated the effect of various substances on the testosterone level in the anesthetized rat and concluded that depression of testosterone secretion was due to catecholamines (and "permissive" cortisol).

Allison et al. (1967) reported results indicating that surgery is associated with failure of the insulin response to glucose load. They compared this effect with the similar phenomenon found in the first 12 hours after myocardial infarction and suggested both are part of a nonspecific, adrenaline-mediated response to stress.

The clinical significance of this stress-induced temporary diabetic state is further considered by Allison et al. (1969). They argue that the biochemical abnormalities they observed, which include a rise in blood sugar and plasma free fatty acids, are attributable to the emotional stress of being brought to operation and the physical stress of the surgery itself, rather than to the effects of anesthesia.

When a patient regains consciousness, the metabolic changes caused by sympathetic dominance under surgical stress are gradually reversed. Contributing to this restoration of homeostasis is a rebound anabolic process that can be speeded by administration of anabolic steroids. Tweedle et al. (1973) give this description of patients' accelerated recovery:

> A single intramuscular injection of an anabolic steroid on the day after operation improved significantly the post-operative nitrogen balance of male patients after truncal vagotomy and pyloroplasty for duodenal ulceration. This effect was evident in both the catabolic (days 1-4) and the anabolic (days 5-8) phases of the response to trauma. The greatest improvement in nitrogen balance was obtained by the combined use of parenteral nutrients and the anabolic steroid.

By increasing the ATP level this measure also diminishes the risk of postsurgical thrombosis. It is important that patients move about as soon as possible after surgery since we know that lack of physical activity decreases testosterone production.

Keele and Neil (1982) also comment on the value of anabolic steroids in the treatment of patients before and after severe surgery, which involves all the same changes in variables that are the hallmark of CVD. When Keele and Neil mention

the value of administering anabolic steroids to these patients, they do so in accordance with their doctrine, which I quote: "Cortisol promotes catabolism of proteins. Normally this breakdown of protein is counterbalanced by anabolic processes but excess of cortisol causes a negative nitrogen balance." Ganong (1975, p 220) also endorses administration of anabolic substances where there is a lack of anabolic processes.

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# Increasing Testosterone and Decreasing Cholesterol by Physical Training

The influence of exercise on carbohydrate metabolism and on the circulation is well known. It is established, for instance, that insulin dosage must be adjusted according to the activity of the diabetic patient: the more active, the smaller the dose of insulin required (Ganong 1975).

The need in CVD is to improve carbohydrate metabolism, one consequence of which is the decreased cholesterol level. Exercise is beneficial in both respects. Improvement of carbohydrate metabolism and decrease of cholesterol level can also be achieved by testosterone; and it has been suggested that the effect of exercise is mediated by this anabolic steroid. Remes et al. (1979) are among those reaching this conclusion. They write: "Physical training can increase endogenous androgen production and it is partly by this mechanism that the beneficial effects of training may be achieved." Numerous investigations on animals confirm these findings.

The problem in its entirety is well appreciated by Aakvaag et al. (1978), who observed the effects of prolonged physical and mental stress on young men undergoing combat training. Initially, testosterone levels fell and cortisol levels rose. Although this is a period of dysstress, it produces rebound parasympathetic activity and is still under the control of natural physiological homeostasis. This was followed by increased testosterone production (eustress), which eventually rose to a level higher than before stress began. In detail, the initial fall in testosterone was from an average of 5.6 ng/ml to a nadir of 0.9 ng/ml on day five. After 6 h sleep on day six, the mean value of 1.8 ng was already significantly higher than the day before. And on day twelve, the observed level of 6.9 ng/ml was significantly higher than on day one. This level of testosterone was maintained at least over the next six days. Investigations show physical training also has the direct effect of decreasing the cholesterol level, which we would expect because of increased testosterone production.

The positive effects on the circulation of testosterone and of physical training are clearly linked. Efficient functioning of the striated muscle is of the utmost importance to all life-maintaining processes, and the skeletal muscles have a decisive influence on the circulation. As has been mentioned, physical activity releases catecholamines, which affect myocardial function. If exertion is excessive (dysstress), tissue hypoxia can arise from the extreme demand for oxygen. However, if physical activity is limited, so that hypoxia is avoided, both skeletal and cardiac muscles can be exercised in a beneficial way. Vagal tone is increased, stroke volume rises, oxygen is used efficiently, and testosterone production increased.

As Ganong writes (1975, p 421): "One of the differences between untrained individuals and trained athletes is that the athletes have lower heart rates, greater end-systolic ventricular volumes, and greater stroke volumes at rest. Therefore, they can potentially achieve a given increase in cardiac output without increasing their heart rate to as great a degree as an untrained individual." He continues,

"Trained athletes are able to increase the oxygen consumption of their muscle to a greater extent than untrained individuals. Consequently, they are capable of greater exertion without increasing their lactic acid production and they contract smaller oxygen debts for a given amount of exertion." The beneficial effect of training is that less catabolic drive is required. Such potentially adverse effects of catabolism as decreased pH (see Ganong 1975) and decreased fibrinolytic activity (see Winther 1966) are therefore avoided.

Physical activity and testosterone are also linked in their beneficial effect on anaerobic metabolism. Remes et al. (1979) showed that six months physical training increases total red cell volume and red cell 2,3-DPG (diphosphoglycerate) concentration. During the same period, plasma testosterone level also increases very significantly, by 21%. The mean increase was greater in subjects in good physical condition: plasma testosterone rose by 43% in the ten fittest subjects, but by only 13% among the ten in worst condition. The overall rise in testosterone levels was accompanied by a significant increase in maximal oxygen uptake, and Remes et al. suggested that hormonal adaption underlies the increased aerobic power. Indeed, it is known that testosterone as well as physical activity increase 2,3-DPG (Ganong 1975; Parker 1972). Further evidence that exercise and enhanced testosterone production can be equated comes from the finding that they have a similar effect on fibrinolytic activity (Winther 1965, 1966).

Nevertheless, despite all the value of physical activity, fanatical propaganda in its favor can have negative effects by encouraging feelings of anxiety or guilt in some people unable or unwilling to exercise. There must also be a warning against excess. One argument runs that if a little exercise is a good thing, then a lot of exercise is better still. This is a fallacy. Excessive exertion can lead to dysstress, with potentially fatal results. The level of activity engaged in by many people in the course of their daily lives is often sufficient for them to achieve a ripe old age without abnormal impairment of the circulation.

For many years my attention and interest have been drawn to individual physical training, supervised by physicians, who must adjust the training to suit each particular case. I started a clinic along these lines in the 1960s. Today, the clinic is visited by more than 3000 people every week. In this way I have personally been able to study the effects of physical training on the circulation, and have observed two changes in particular: increased fibrinolytic activity (Winther 1965, 1966) and decreased cholesterol level. It should not be necessary to add that physical training, if well adjusted to the individual, has psychological benefits, increasing feelings of comfort and well-being. This too is a function of the autonomic nervous system, which governs the circulation.

# The Negative Nitrogen Balance

A shift towards a negative nitrogen balance implies impairment of essential life processes. Among the substances adversely affected are:

- Enzymes in the Krebs cycle, resulting in impaired carbohydrate metabolism and anaerobic metabolism, with a consequent deterioration of the circulation
- Transport proteins in blood plasma, such as hemoglobin and lipoprotein
- Contractile proteins like actin and myosin
- Connective tissue
- Antibodies
- Insulin

In cases where natural homeostasis is lacking, administration of testosterone can counteract a negative nitrogen balance. The idea of this chapter is to emphasize the significance of negative nitrogen balance in connection with CVD.

A very interesting article by Sobel and Marmorston appears in a book edited by Pincus and published in 1958. Briefly, the article puts forward the following theory: ageing is a time-associated biological phenomenon accompanied by several changes, the progression of which leads to a failure in the maintenance of vital energy and finally to death. It is the authors' opinion that these changes are dominated by anti-anabolic influences and that they are irreversible. The authors' conception corresponds to my line a in Fig. 2. There is, nevertheless, an undertone which suggests that there is an area of reversibility present, which is subject to control. This conforms with my line b.

Sobel and Marmorston discuss the role of the two fractions of connective tissue — ground substance and collagen — in the ageing process and in disease. Every cell in the body except those floating in the bloodstream is dependent upon connective tissue for contact with its external environment (Fig. 4).

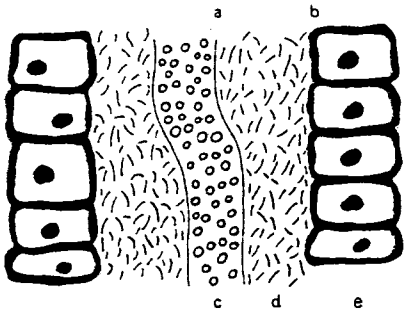



**Fig. 4.** Schematic drawing illustrating the important location of connective tissue (*d*) between the capillaries and parenchymal cells (*e*). *a* Capillary membrane, *b* cell membrane, and *c* blood.

It is through the connective tissue (the hexosamine fraction in particular) that oxygen and nutrients reach the cells and by way of this medium that waste products are removed. The authors suggest that a decrease in the hexosamine – collagen ratio (H/C) causes the ageing process. It has been known for a long time, from histological observations, that there is an increase in fibrillar density with age, such that this increase in quantity of collagen will exceed that of the constituents of the ground substance.

Sobel and Marmorston have administered *cortisone* to rats. A decrease in *hexosamine* content is observed. However, this is not the case with collagen. The result is a reduction in the hexosamine – collagen ratio. When cortisone treatment is stopped, partial or complete recovery of the H/C ensues. This provides proof that hexosamines are part of the metabolic pool. It shows that in the presence of a state such as CVD, which induces negative nitrogen balance in the organism, the soluble constituents of the ground substance may be drawn upon but the fibrillar components considerably less so, these components being relatively metabolically inert. A decrease in H/C shifts the balance towards anaerobic metabolism, the root of CVD, because of decreased oxygen supply to the tissues.

The intuitive association of the ageing syndrome and its disturbed protein metabolism with the loss of gonadal activity render it probable that androgens can cause the retention of nitrogen. This was confirmed, scientifically, by Kochakian and Murlin (1935), who demonstrated that androgens can cause the retention of nitrogen in castrated dogs. This led Sobel and Marmorston to ask what effect the cortisol-testosterone ratio has on connective tissue. They show that an increase in this ratio is a decisive factor in the ageing process and that decreased testosterone production raises the susceptibility to arteriosclerosis and follows myocardial infarction. The cortisol – testosterone ratio in CVD patients aged 40 was found to be the same as in normal women of 80.

Sobel and Marmorston conclude their article by saying,

> These studies have no more than dented the surface of a vast, intricate problem. Perhaps they will one day help us to understand some of the factors which in the ageing process of man cause dissociation of chronological time from biological time and the well-known observation that life experiences play a role in establishing this dissociation. In referring back to our definition of ageing, perhaps the slight note of optimism contained therein does not seem unfounded.

The cortisol-testosterone ratio discussed above by Sobel and Marmorston is a subject that has interested many renowned scientists. Selye (1969) considers myocardial infarction caused by corticoid pretreatment in animals, and concludes that this necrosis can be prevented by chemical agents which act on the myocardium directly (as cortisol does). Today we know that the chemical agents which act directly on the myocardium are the anabolic steroids which antagonize the effect of cortisol.

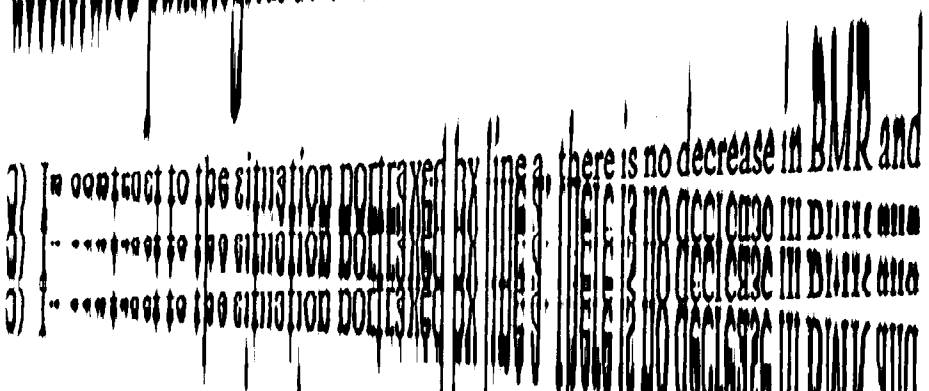
I am not fully aware of what inspired Sobel and Marmorston to concentrate on these two hormones. I feel tempted, though, to assume that they were never engaged in clinical work, let alone in the treatment of CVD. From stating that the cortisol-testosterone ratio in patients aged 40 is the same as in normal individuals aged 80, it should be a short step to recognizing the value of testosterone in the treatment of CVD (because testosterone increases the hexosamine fraction, facilitating the transport of oxygen and nutrients to the cell). Yet it is not a step that Sobel and Marmorston take. Their merit is that they have participated in the scientific explanation of testosterone treatment for CVD, which had already been used for decades.

Like Sobel and Marmorston, I have stated that two biochemical agents, cortisol and testosterone, play a decisive role in the metabolism, cortisol breaking down protein and testosterone building it up. It is not only testosterone production that decreases with age. This happens also with cortisol production, although to a lesser degree. If a decrease in cortisol production did not take place, our life expectancy would be less than it is. Cortisol production is inversely proportional to life-time, so to speak.

On line a in Fig. 2 cortisol production is endogenous and genetically determined, and cannot be altered in a positive direction, since to do so would imply that we are able to prolong life indefinitely. On line b, however, cortisol production is *also exogenously* determined. It is largely under the influence of civilization-induced emotional and environmental stresses, and also of both naturally available and administered testosterone. I maintain that this anabolic substance is a factor that can counteract the effect of the life experiences that play a role in CVD development (in the next chapter we will look more closely at how the negative nitrogen balance is a crucial factor in CVD). The cortisol production represented by line b is, therefore, a metabolically adjustable factor. This relation has inspired many scientists to concentrate their research on cortisol as a pathological factor in CVD, and on the positive effect of testosterone on the circulation in the spirit of Sobel and Marmorston.

## Effect of Negative Nitrogen Balance

The overproduction of catecholamines and cortisol plays a central part in the deterioration of the circulation. Under normal conditions catecholamines promote the production of glucose from glycogen. When the glycogen depots are depleted cortisol breaks down protein to amino acids which form glycogen to be drawn upon by the catecholamines. This is a part of normal carbohydrate metabolism. Stress-situations, however, induce an overproduction of catecholamines with an increased glycogen breakdown. In order to keep step with this breakdown cortisol accelerates its action on *protein* to maintain a sufficient supply of glycogen for glucose production. Along the slope of line a, catecholamine increases and the circulation deteriorates correspondingly (as indicated in Table 1 and 2). Individuals on this path show a decrease in BMR and physical activity. Line b reflects an accelerated increase of catecholamine production, and the accelerated pathological deterioration of the circulation associated with it (Table



2). In contrast to the situation portrayed by line a, there is no decrease in BMR and physical activity on line b. The individual on line b therefore has a level of physical activity (and BMR) that is too high in relation to his oxygen supply. This is not the case for someone on line a, whose activity corresponds to his oxygen supply (though, of course, any increase in exertion will cause the person to end up like the patient on line b). The negative nitrogen balance has an overwhelming significance for CVD. Protein, which is the core substance of the body, is consumed. Our aim is to counteract the process with testosterone.

## Excess of Cortisol

"Normally (this) breakdown of protein is counterbalanced by anabolic processes but *excess of cortisol causes a negative nitrogen balance*....Cortisol excess raises blood lipids and the plasma cholesterol level. This leads to arteriosclerosis" (Keele and Neil 1982. Emphasis added). This textbook confirms that excess of cortisol leads to a negative nitrogen balance and hence to CVD. The underlying biochemical processes are as follows: cortisol breaks down protein to amino acids from which glycogen is formed by the activation of the appropriate enzymes. Glycogen is further broken down to glucose by catecholamines. In the case of CVD there is an *excess* of cortisol and catecholamines. The aim now is to inhibit the effect of the overproduction of catecholamines and cortisol, which causes impaired carbohydrate metabolism. This can be achieved by inhibiting the effect that cortisol has on the glycogen production. Thus, the aim is to inhibit the insulin antagonist cortisol in order to improve the carbohydrate metabolism. This is done with testosterone.

## Administration of Testosterone

By promoting protein synthesis, testosterone diverts amino acids from glycogen to protein production and so also improves carbohydrate metabolism. This is one way of explaining the regulatory mechanisms of testosterone. Another explanation is offered by Ganong (1975) who writes, "Following the administration of anabolic steroids, such as *testosterone*, nitrogen intake exceeds excretion and *nitrogen balance is positive*" (emphasis added) – and the state of CVD thereby improved.

Using testosterone in the treatment of CVD we achieve positive results with one of the body's own self-regulatory products and so restore homeostasis. Altogether, this is an ideal approach to solving the problem.

# Evaluation of the Parameters of CVD

Despite the superior results obtained by hormone treatment for deteriorated circulation, we face difficulties in accommodating them to the narrow statistics of clinical trials. Describing the situation in my clinic is worth many such trials. Many patients are sent by their own doctors because of their deteriorated circulation. They consult me primarily about limb pain and restlessness at night that keeps them from sleeping. I am able to help the majority of these patients by hormone treatment. Because they have begun treatment in time, they avoid 'stage 3' of the disease (see p 13). When returning for subsequent check-ups they feel well in every respect to the point of euphoria, and they are now able to sleep at night. This relaxaton is of the greatest importance in order to counteract the deterioration of the circulation.

These results are, however, more or less subjective and cannot, therefore, form the basis for a statistical evaluation. Biochemical variables related to CVD, however, are objective and can be used statistically. This has already been done by the WHO, which states, for instance, that testosterone treatment causes a "significant fall in serum cholesterol." The University of Copenhagen has shown a decrease in cholesterol level in 83% of 300 patients treated with testosterone, and the University of Roskilde found a decrease in nearly 100% of similar cases.

Other parameters could just as easily have been chosen for investigation, since they improve in parallel after testosterone treatment. However, cholesterol reduction is an appropriate criterion to use since some in the medical world have been hypnotized by it to the extent, one might add, of using drugs like clofibrate — with fatal results. These people would have done better to act in the way suggested by the WHO, which indicated use of testosterone to decrease cholesterol. A difference between testosterone and clofibrate is that (as the WHO report shows) testosterone not only decreases cholesterol level, but *also* increases fibrinolytic activity (favoring aerobic metabolism) and decreases platelet adhesiveness (increasing ATP production and normalizing impaired carbohydrate metabolism). In other words, it improves all the interacting parameters of CVD, in accordance with my cog-wheel theory. Again I stress that *the only scientific way to proceed is to improve every parameter involved.*

The WHO report mentions use of phenformin in connection with anabolic steroids. However, it should not be necessary to point out that phenformin does not contribute to the improvement of the different parameters listed in the Madrid report (WHO 1972). The same improvement has been achieved in medical centers with anabolic steroids alone. Phenformin has no effect on CVD parameters.

### Further Comments on Evaluation of Parameters

A publication by The National Health Service of Denmark (1978) lists the distribution of causes of death in age groups by sex. It is evident that up to the menopause fewer women than men die of heart disease. Hereafter there is no

difference. The report states that the incidence of heart disease increases gradually in the last decades of life and accelerates dramatically in the oldest age groups.

If it is maintained that CVD is a "disease" in the usual sense of the word, statistically evaluated clinical trials must include the whole group, young and old. In older people, who are the biggest age group, the physiological factor is increasingly important and becomes more dominant than the pathological factor. As the physiological factor is refractory to treatment, the statistical results of such trials may give the completely wrong picture that testosterone treatment is not effective in a sufficient number of cases. An absolute condition for anyone participating in the discussion of CVD must be that he has at least some clinical knowledge. Everybody that I have met till now who proposes statistical evaluation has never dealt clinically with CVD patients, and they compare this ailment with other diseases where it is possible to conduct ordinary clinical trials. This shows that they have not understood the true nature of CVD. If trials were carried out on these false assumptions, the conclusion would be that the young people are the victims even though the pathological factors dominate in their case, and it has been scientifically proven that this factor is counteracted by testosterone treatment.

Man appears to have a genetically determined lifespan for a finite period of time. Ageing involves two main processes: time-related, involutional physiological changes and disease or stress-induced pathological changes. The physiological factor is beyond our influence; counteracting it would imply that we are able to prolong life indefinitely. Our goal is to counteract the pathological factor.

Before ending this section I shall not refrain from mentioning that great doubt has recently been raised as to whether this statistical level is really as high as claimed. In the United States, the Surgeon General's report (Department of Health, Education, and Welfare 1979) stated that about 40% of the entire population will die from heart disease and approximately 80% of these deaths will occur between the ages of 65 and 100. Of the remaining 20%, probably half will have hereditary problems of lipid metabolism, diabetes, and hypertension that require comprehensive care. This leaves about 4% of the general population without readily identifiable defects who will die of heart disease before the age of 65.

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# Comments on Photographs



I will now briefly summarize the underlying biochemical processes that lead to a deterioration of circulation and to its restoration by testosterone.

The Krebs cycle is the process relating the metabolism and interconversion of fats, carbohydrates, and proteins. However, before these nutrients can enter the cycle their carbon backbones must be degraded so that they yield the acetyl groups of acetyl CoA, the form in which the citric acid cycle accepts most of its fuel input (Lehninger 1982).

Under normal conditions the catecholamines and cortisol are in equilibrium with insulin, which conducts glucose into the Krebs cycle. However, situations may occur during life which cause a particular overproduction of catecholamines and an ACTH-stimulated rise in cortisol. The result is breakdown of protein by cortisol and its conversion to carbohydrate by catecholamines at a rate faster than would be normal for a person of that age.

This radical attack on protein, the core substance of life, causes inactivation of enzymes necessary for normal aerobic metabolism. The amino acids produced from protein breakdown form glycogen which is further broken down by catecholamines into plasma glucose. In this way, excess catecholamines and cortisol act as insulin-antagonists, inhibiting glucose uptake by the tissues and impairing carbohydrayte metabolism. As a result of this there is insufficient oxaloacetic acid in the Krebs cycle for the oxidation of acetyl CoA. The increased plasma lipid concentration that results leads to a raised plasma cholesterol level, in other words, to deteriorated circulation, i.e., CVD.

The circulation starts in the heart. With overproduction of catabolic substances there is decreased oxygen supply to the tissues and to the heart itself. This can be seen from ischemic changes, with or without loading, on the ECG. The deteriorated circulation that begins in the heart manifests itself in the periphery where it may cause gangrene, as seen in the photographs, and of course is responsible for myocardial infarction.

Widespread investigations show that testosterone counteracts hypoxia of the heart, preventing infarction as well as gangrene, and normalizing ST segment depression on the ECG. On the basis of this evidence I repeat the question asked at the EOCCD meeting in Munich in 1985: "Why not use testosterone before subjecting patients to the risk of heart surgery with doubtful results?"

I have illustrated by means of photographs, how postheparin lipoprotein lipase, activated by testosterone, leads FFA into Krebs cycle, thus regulating impaired carbohydrate metabolism and thereby improving the circulation in CVD patients. The tests were carried out on a group of patients at regular weekly intervals. The photographs shown here (Fig. 1) are typical of the results in patients and show how the creamy plasma, containing triglycerides, gradually becomes clearer during testosterone treatment as a result of a decrease in plasma lipid concentration.

The photographs of the test tubes show processes that take place "inside the body," so to speak. In contrast, Figs. 5 and 6, for instance, show what can be seen

by looking at the patient "from the outside". The first photographs demonstrate the gangrene that results from the overproduction of cortisol and catecholamines. Figures 7 and 8 provide overwhelming and fascinating evidence of how administration of testosterone heals the gangrene. This has been its effect on thousands of patients and it has saved them from amputation.

It cannot be emphasized strongly enough that these results have been achieved without any form of fanatical selective dieting, based, for example, on the foolish idea that margarine is "healthier" than butter; and without prescribing exaggerated physical activity, which is more likely to kill the patients than cure them.

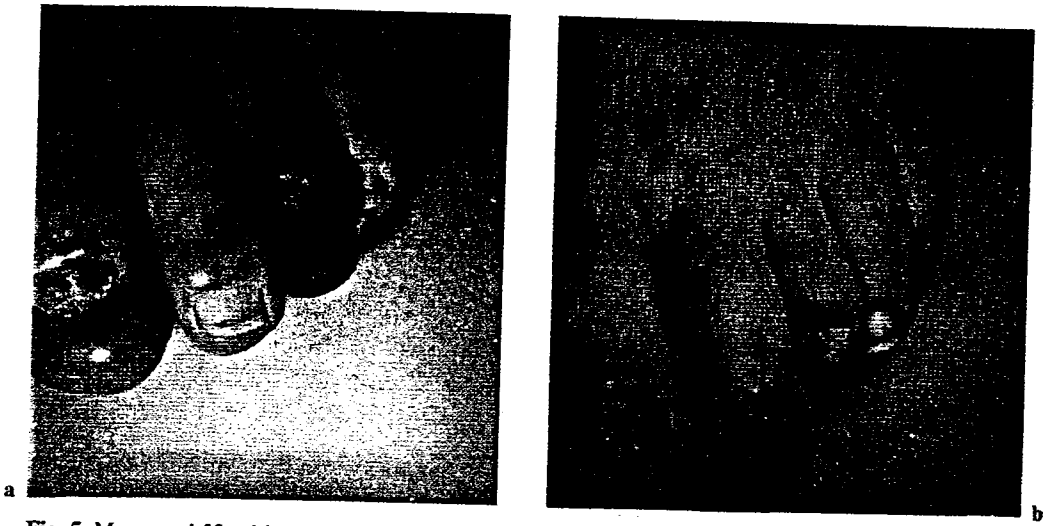
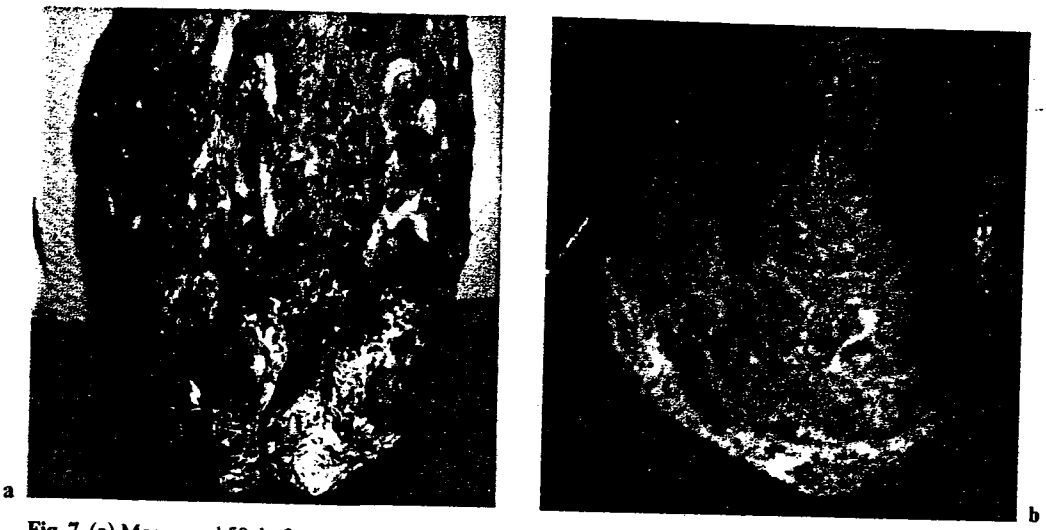


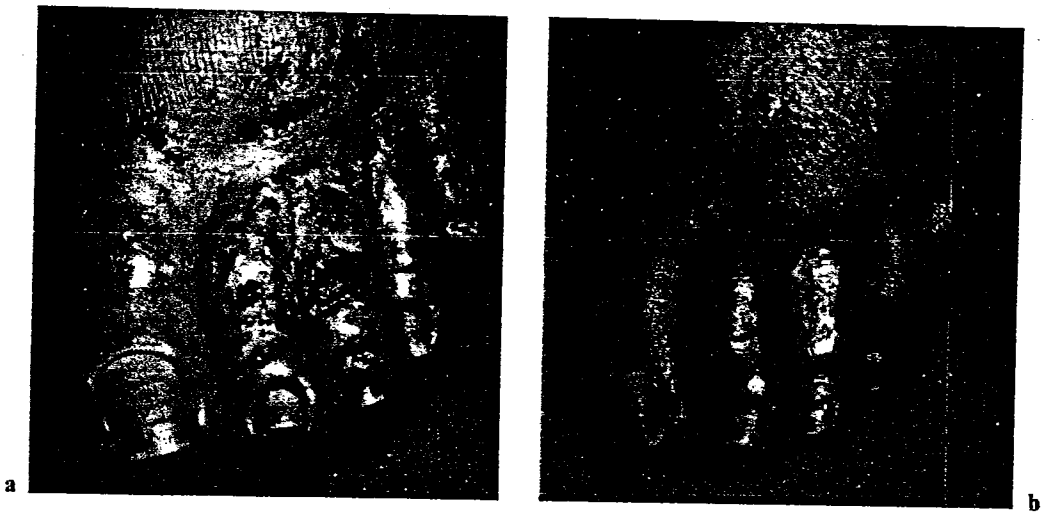
**Fig. 5.** Man, aged 55, with gangrene of the left 1st and 3rd toes for which amputation of the left leg had been advised. The left foot before (**a**) and after 3 months of treatment (**b**).

**Fig. 6.** Man, aged 77, with gangrene of all 5 toes. (**a**) Before treatment and (**b**) after 3 months. Ulceration healed completely.



a b

**Fig. 7.** (a) Man, aged 50, before treatment. (b) After 5 years of continuous treatment the gangrene healed completely.



a b

**Fig. 8.** Diabetic woman, aged 85, before treatment (a) and after 1 year of treatment (b).

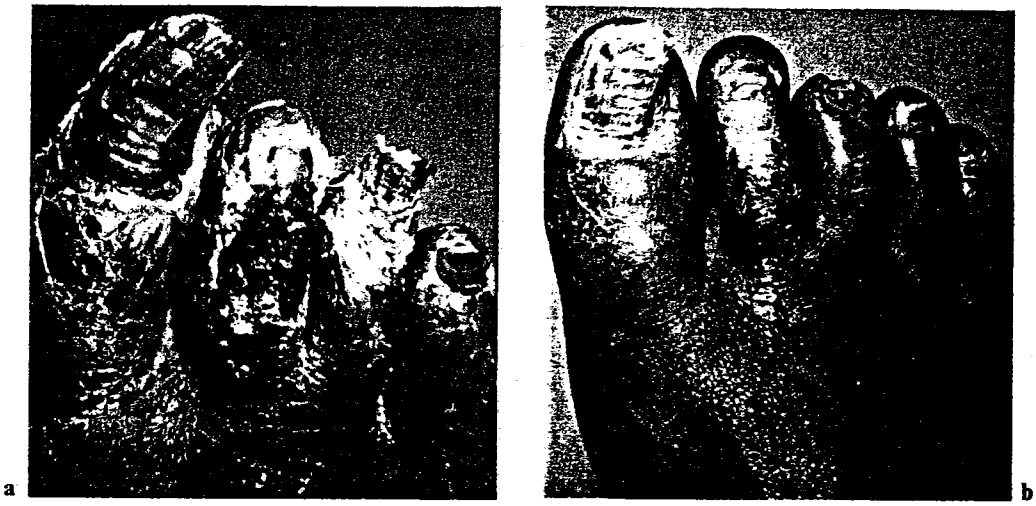


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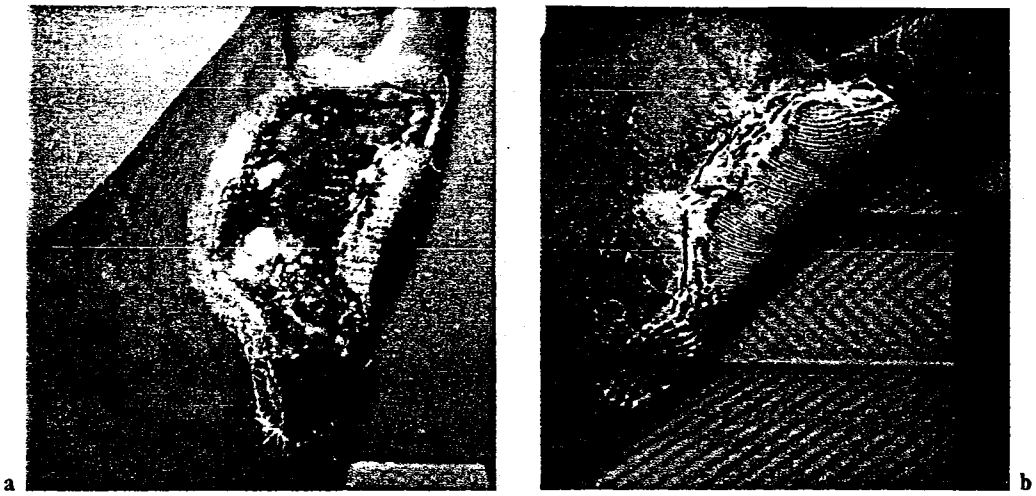
**Fig. 9.** Man, aged 57, before treatment (a) and after 5 months of treatment (b). Gangrene had developed after sympathectomy.



a b

**Fig. 10.** Diabetic man, aged 77, before treatment (a) and after 8 months of testosterone treatment (b).

# The Balance Between Hormone Sensitive Lipase and Postheparin Lipoprotein Lipase

A struggle is waged between hormone sensitive lipase (activated by catecholamines and cortisol) and postheparin lipoprotein lipase (activated by testosterone). Under normal conditions there is a balance between these two lipases. During stress the activity of hormone sensitive lipase rises, causing a shift towards anaerobic metabolism, which means increased plasma glucose, FFA, and acetyl CoA. Due to lack of oxaloacetic acid, acetyl CoA cannot enter the Krebs cycle, but is synthesized to cholesterol. A rise in cholesterol is, therefore, a sign of the anaerobic metabolism leading to CVD. This is in accordance with what is said elsewhere in this book that there is a continuous struggle between testosterone and cortisol, and the state of this struggle is reflected in the level of cholesterol.

By the administration of testosterone, postheparin lipoprotein lipase is activated. The chylomicrons are cleared from plasma and the triglycerides stored in the fat depots for normal metabolic utilization, the natural homeostasis of the organism is facilitated, and the equilibrium between the two lipases is restored. This decreases the cholesterol level and counteracts CVD.

Apart from activating hormone sensitive lipase during stress, the overproduction of catecholamines has another effect: it depletes liver glycogen. The consequence is a rise in plasma glucose. In order to keep step with the depletion of glycogen, an excess of cortisol accelerates gluconeogenesis in the liver mainly by favoring glycogen formation from amino acids formed by protein breakdown. Testosterone builds up protein. Consequently, administration of testosterone inhibits protein breakdown and thereby contributes to the restoration of homeostasis. In a normal aerobic situation where liver glycogen level is high, the rate of deamination of amino acids is depressed. Therefore, amino acids remain available for protein synthesis.

The photographs in this section of this book also reflect the struggle between the two lipases. The photographs on the left illustrate the situation in which hormone sensitive lipase dominates and gangrene has developed. The photographs on the right represent a state in which postheparin lipoprotein lipase, activated by testosterone, counteracts this dominance, reestablishing a balance. It is important to bear in mind, however, that the extent of gangrene is not directly related to the seriousness of CVD. A more accurate reflection of the state of the circulation is given by the biological and physiological parameters we have discussed. Breier et al. (1985) consider one parameter — the post-heparin lipoprotein lipase — and say, "The extent of coronary-artery disease is thus strongly influenced by an LPL (post-heparin lipoprotein lipase) deficit. LPL activity correlated with plasma testosterone...."

Whichever model we employ to describe the metabolic changes leading to CVD, the positive effect of testosterone manifested by the normalization of pathological signs on the ECG (see Breier et al. 1985) and healing of gangrene (most strikingly illustrated by the photographs in this book) are the same. Different descriptions are simply a useful means of clarifying the pathogenesis from more than one angle and facilitating the reader's understanding of this multifaceted problem.

Dosage depends on how each individual patient responds to treatment and is a matter of clinical experience. In severe cases of CVD I start by giving testosterone depot 250 mg three times per week to men and 100 mg per week to women. Side effects may occur in the form of edema in association with sodium chloride retention. This is satisfactorily counteracted by diuretics. In cases of edema and polycythemia a short pause in treatment is required. Female patients may in some cases experience vocal changes and hirsutism. For this reason I try to achieve results with the lower dosage of 100 mg. Almost all my female patients are postmenopausal and already exhibit signs similar to these side effects. They are, of course, warned about them before treatment is started, but are willing to run the risk of developing the side effects, since in the hospital they have been threatened with amputation. By no means all female patients experience side effects, which may be avoided by decreasing the dosage when improvement of circulation begins.

Several renowned publications report how healthy young men experience decreased sexual activity when given testosterone. There are good reasons why this should be so from an endocrinological point of view. However, my young male *patients* never complain about decreased sexual function when treated with testosterone. The explanation may be that they have a need for a supplement of testosterone because of their CVD. Nevertheless, when I question male patients about their sexuality and hint at impotence and lack of erection some of them are very surprised that I raise this problem since they had themselves noticed that they began to feel less sexually active at the same time their circulatory disorder started.

Endogenous testosterone only has an effect on the tissue of muscles and vessels if the individual is physically active. This is also true for administered testosterone. For this reason, patients are advised to move about to the limit of pain, but not any further. Leg cramp and angina pectoris are warnings of gangrene and infarction (dysstress). These circumstances make it even more difficult to help patients in stage 3 of CVD, i.e., those with gangrene. Such cases usually require patience and large doses for a long period. It is obvious that treatment of very old patients must necessarily be more and more difficult as they are nearing the end of their life-span compared to patients who have a long life-span ahead of them. Another point of importance is that the physiological factor which is refractory to treatment increases constantly.

Women of fertile age who have undergone an ovarectomy and then develop CVD symptoms often respond very positively to treatment with a mixture of testosterone and estrogen given, say, once a month.

It is imperative that patients eat sufficient protein when treated with testosterone. This factor is strongly stressed by many investigators (see for instance Gudbjarnason 1972). A mixed diet, containing vegetables, with a supplement of vitamins A, B, C, and E, each vitamin administered separately, is advisable. During treatment any form of medical stimulant must be reduced to an absolute minimum and patients are urged to stop smoking and drinking alcohol.

In my experience there is a connection between testosterone and the pigmentation of the skin. Female patients are asked how they react to sunlight. If they get sun*burned* and not sun*tanned*, they generally respond more rapidly to treatment and have no side effects. The same phenomenon is true for patients with certain kinds of vitiligo. The relationship between testosterone and skin-pigmentation is well-known. For instance, castrated men often have a skin with a characteristic pasty, sallow color, grey and lacking in pink tinge. When treated with testosterone they present a more tanned appearance, particularly of the most exposed parts of the skin (Hamilton and Hubert 1938). It is also interesting that there is an increase in androgen secretion in connection with quartz-light treatment (Myerson and Neustadt 1939). Some male patients suffering from untreated dystrophia adiposa genitalis have also consulted me for CVD.

Prophylaxis of CVD is a very delicate and difficult subject to deal with. To interfere with habits often proves almost impossible. We know that people achieve a ripe old age without taking any special precautions. A piece of good advice is that people should keep in good shape, maintain normal weight, stay physically active, and avoid the kind of stimulants already mentioned.

In 1977 Lord Henry D. Walston, who has always taken special interest in the problem of CVD, invited me to the House of Lords to speak as the representative of the medical profession at a lunch-meeting in the Cholmondeley Room. Present were politicians and scientists from all over the world. In the discussion that followed with colleagues from universities in Japan I learned that they use testosterone *prophylactically* once they find the same biochemical abnormalities that I do in cases of CVD, even though their patients are clinically asymptomatic. However, the way I look upon testosterone treatment of CVD does not, at the present time, provide a basis for prophylactic testosterone therapy.

We must always bear in mind when treating CVD that we are fighting two factors: inevitable ageing processes and pathological processes. As stated above, it is not generally possible to distinguish between physiological and pathological deterioration of circulation. If age-related physiological processes could be excluded we would be left with only the *pure* disease-related processes, on which we could then examine the *true* effect of testosterone. However there is a specific circumstance in which this can be done: an individual undergoing surgery has, *temporarily*, the same biochemical abnormalities as are found in CVD, such as a rise in blood sugar and FFA and a negative nitrogen balance. (See the section "Use of Anabolic Steroids in Surgical Stress"). A single intramuscular injection of testosterone on the day after operation has been shown to improve postoperative metabolic changes significantly. The positive results that we can see in the laboratory tests are the effect of administering an anabolic substance to an organism that has been subjected to stress and temporary deterioration of the circulation (i.e., CVD, showing exactly the same biochemical abnormalities). Adding this observation to the positive results seen in the CVD patient completes the scientific basis for the testosterone treatment of deteriorated circulation.

The situation mentioned above is a real in vivo experiment, without the influence of the irreversible involutionary processes, in which there is an overnight demonstration of the effect of testosterone on the deteriorated circulation after surgery. Without testosterone and if natural homeostasis is not sufficient, the development of such postoperative abnormalities would be fatal. This "natural experiment" justifies my concept of dividing CVD into physiological and pathological processes, as illustrated in Fig. 2 by line a and b.

Let us then compare the two situations, that of surgery and of CVD.

Surgery involves:

- Acute subjection to stress
- Biochemical abnormalities leading to deteriorated circulation (temporary CVD)
- Prompt improvement of the abnormalities by administration of testosterone
- Overnight improvement in laboratory tests

CVD involves:

- Acute or chronic subjection to stress
- The same biochemical abnormalities leading to deteriorated circulation (chronic CVD)
- Protracted improvement of the abnormalities, due to intervention with the physiological factor testosterone
- Gradual improvement in laboratory tests

Surgery, which can lead to fatal deterioration of circulation, can be compared with fatal myocardial infarction precipitated by a sudden outburst of intense anger or severe exertion. If such a case is not fatal, administration of testosterone can restore the circulation just as the anabolic injection counteracts the postsurgical abnormalities.

The result of testosterone treatment of CVD is even more remarkable when we consider that we counteract the disease-related factor *even though* it is superimposed on the irreversible age-related factor, which naturally delays the positive outcome of treatment.

# The Ultimate Involution of the Biological Functions

This book has dealt with aerobic metabolism, and more especially, with anaerobic metabolism, which leads to CVD. I have attempted to describe the deterioration of circulation causing the extinction of life.

CVD is a consequence of anaerobic metabolism, impaired carbohydrate metabolism, and overproduction of catecholamines. Anaerobic metabolism means decreased testosterone production and therefore decreased activity of postheparin lipoprotein lipase and increased activity of hormone-sensitive lipoprotein lipase. This results in a stream of free fatty acids pouring from fat depots into the plasma, and in a surplus of acetyl CoA. The supply of oxaloacetic acid is inadequate relative to the formation of acetyl CoA, which therefore cannot be completely metabolized by the Krebs cycle. The supply of acetyl CoA thus increases. Acetyl CoA units do not condense to form ketone bodies. (There are three conditions which may lead to ketone body overproduction — juvenile onset diabetes, starvation, and a high fat low carbohydrate diet). Nonoxidized acetyl CoA is therefore used for the biosynthesis of cholesterol in lieu of its conversion to fatty acids, because the pathway to fat depots is blocked by hormone-sensitive lipoprotein lipase, and the cholesterol level rises as a symptom of the deteriorated circulation. An excess of catabolic substances means that cortisol builds up glycogen from deaminated amino acids at a higher rate than normal. This also applies to overproduction of catecholamines which also, at higher concentration, break down glycogen to plasma glucose to be excreted in the urine. Excess of cholesterol is removed from the body by conversion to cholic acid in the liver. When the stress on the body continues, more acetyl CoA is produced, and there is consequently less phosphorylation of ADP and hence less ATP production. Lowering the ATP level to less than 50% results in irreversible necrotic processes in the heart and the circulation breaks down as the final involution in CVD.

# Conclusion

I do not pretend to have completely covered the scientific basis of the biochemical, physiological, and cardiological processes involved in CVD. What is stated in this book is based on extracts from accepted textbooks and authoritative publications concerning CVD. At the same time its truth is proved by the positive effect testosterone treatment has on deteriorated circulation.

I have entitled the book "Cholesterol" to please my opponents, since they seem to be hypnotized by trying to decrease the level of this parameter as a means of helping their patients. However, I must say that our solutions to this problem are — to put it mildly — very different.

The positive results obtained by administration of testosterone for CVD are well recognized. Therefore I believe that the time is ripe to realize my "pyramid" idea: the delay in the utilization of testosterone for CVD has arisen from a failure by specialists in endocrinology, biochemistry, physiology, and cardiology to understand one another's points of view and therefore to coordinate their clinical efforts effectively. This is like four people starting to climb the various faces of a pyramid, unaware of each other's presence until they reach the apex. It is hoped that bringing specialists in these different disciplines together at "summit meetings" will help them discover the true nature of this disease, the cardiovascular specialist understanding the underlying lack of the anabolic factor in the metabolism and the other three grasping the way in which treatment with anabolic steroids can effectively counteract the metabolic disturbance which is the cause of CVD. As President of the EOCCD I am convinced that I can persuade this organization to support such cooperation as a contribution to medical research and for its benefit to patients.

# Exchanges of Views on the Themes of the Book

## Discussion with Malcolm Carruthers

Malcolm Carruthers, M.D., F.R.C.Path., Ph.D., M.R.C.G.P., has spent 15 years researching the biochemical changes and autonomic imbalance underlying CVD and has written many scientific articles and several books on the subject. Carruthers had the opportunity to read the outline of this book. Stimulated by the arguments presented, he asked Møller, whom he first heard describe his approach to the problem during an EOCCD symposium in the House of Lords in 1977, about some of the important questions raised.

Carruthers: I understand that your theories imply, briefly, that CVD is caused by anaerobic metabolism, due to excess catecholamines and cortisol. Consequently there is impairment of many biochemical functions — a situation which can be counteracted by testosterone, restoring aerobic metabolism and improving the circulation. This relates to the basic physiological equation *heart rate* × *stroke volume* = *cardiac output*. The equation explains how a rise in the production of catecholamines can maintain adequate output in the face of decreasing stroke volume by an increase in heart rate. In other words, if stroke volume decreases, sympathetic dominance will develop.

Møller: Let me state, first of all, that my theories are founded on the support of established biochemical and physiological principles and many authoritative publications. Concerning the physiological equation it is essential for the circulation to have a high stroke volume and a relatively low heart rate. Myocardial efficiency decreases in a striking fashion when heart rate rises above a certain point. To use the words of Keele and Neil (1982), "The higher the heart rate, the greater the myocardial $O_2$ usage for any given cardiac output." On the other hand, "Increasing the stroke volume against a constant pressure (heart rate kept constant) does not greatly increase myocardial $O_2$ usage, hence efficiency rises in a striking fashion," (Keele and Neil 1982).

Table 2 also supports my view that a consequence of catecholamine excess is a deterioration of the circulation brought about by increased heart rate. The table shows that coronary mortality is far greater in patients with high postinfarction plasma catecholamine levels. If we increase the stroke volume we pursue our aim of improving the circulation. This can be attained by physical activity and by administering testosterone.

Carruthers: Do the textbooks confirm the relation between physical training and improvement of stroke volume?

Møller: Yes, certainly. In the book I give several references. For instance Ganong writes (1975, pp. 421, 439), "One of the differences between untrained individuals and trained athletes is that the athletes have lower heart rates, greater end-systolic ventricular volumes, and greater stroke volumes at rest. Therefore, they can potentially achieve a given increase in cardiac output without increasing their heart rate to as great a degree as an untrained individual." Sensible physical activity increases testosterone production, decreases catecholamine production, restores aerobic metabolism, raises ATP levels, and improves enzyme activity.

Insufficient movement in daily life causes circulatory deterioration. Every student nurse knows that confining a patient to bed even for a week will inevitably lead to muscle atrophy. Activity of the muscles is the means by which the circulation is kept going.

I return to testosterone. It is well-known that testosterone increases the production of ATP, which explains a shift from anaerobic towards aerobic metabolism. Consequently, testosterone will stimulate the activity of enzymes in the Krebs cycle, where activity was decreased by anaerobic metabolism. The paper by Gudbjarnason et al. (1972) confirms that anabolic steroid administration increases ATP level. You should read Ravens (1970) who says that after induced infarction in dogs, anabolic steroids significantly diminish the reduction of ATP and that this indicates a positive effect of anabolic agents upon the synthetic and mechanical functions of the heart muscle. Furthermore, Seliverstov (1969) states, "After an eight-day long administration of anabolic steroid, the arterial pressure was reduced, the systolic period shortened, diastole lengthed, contractile capacity of the myocardium increased [the proteins actin and myosin depend on testosterone] and the mechanical efficiency of the heart increased without causing any substantial changes in the pulse rate and peripheral resistance."

Carruthers: You are saying that predominance of the sympathetic nervous system, and raised cortisol levels, lead to other negative physiological and biochemical effects on the metabolism and hence on the circulatory system. This is basic physiology, of course, but could you elaborate?

Møller: In the book I have made a special point of how cortisol breaks down protein to amino acids from which glycogen is formed by activation of appropriate enzymes. Glycogen is further broken down to glucose by catecholamines. The consequences of this activation are a rise in the blood glucose and lactic acid levels. As you know, under normal conditions catecholamines and cortisol are balanced with insulin, which conducts glucose into the Krebs cycle. However, *overproduction* of catecholamines and cortisol leads to impaired carbohydrate metabolism. As a result of this there is insufficient oxaloacetic acid in Krebs cycle and therefore increased FFA, acetyl CoA, and plasma cholesterol. Here I have described the CVD situation and the origin of atherosclerosis.

Carruthers: This is a fascinating way to present it. May I again ask for evidence supporting these key biochemical theories?

Møller: Under normal circumstances carbohydrate and fat metabolism have a common meeting point in the citric acid cycle. Acetyl CoA is the chief product of fatty acid oxidation, bringing fat into the carbohydrate pathway. The reverse reaction will synthesize fatty acid by combination of acetyl CoA obtained from pyruvic acid. Thus after the Krebs cycle has taken what is necessary to maintain normal metabolism, any surplus carbohydrate in the diet becomes FFA to be stored for later use. When required, it is turned into acetyl CoA, which can enter the Krebs cycle. With impaired carbohydrate metabolism, surplus plasma glucose cannot enter the Krebs cycle to produce energy, and it cannot be stored in fat deposits either. On the contrary, FFA accumulate; and instead of being deposited they are drawn from the depots due to overproduction of the catabolic hormones catecholamines and cortisol. Because of insufficient oxaloacetic acid, the production of acetyl CoA increases. Since acetyl CoA cannot form depots it is metabolised to cholesterol which, due to lack of oxygen, cannot be fully utilized in the synthesis of hormones, such as testosterone. (Normal production of testosterone is necessary to maintain a healthy circulation.)

These processes are confirmed by Keele and Neil (1961), who say that in the diabetic state (which I have argued is equivalent to CVD) "cholesterol is synthesized from active acetate units in lieu of their conversion to fatty acids, and contributes to the rapid development of atherosclerosis." In other words, atherosclerosis would not develop if the active acetate units entered the Krebs cycle as normal to produce energy instead of increasing the level of cholesterol. We know that cortisol excess leads to a diabetic state and anaerobic metabolism. Again I quote *Samson Wright's Applied Physiology*: "Cortisol excess raises blood lipids and the plasma cholesterol level. This leads to atherosclerosis" (Keele and Neil 1982). The increase in blood lipids is due to excess active acetate units, which can neither enter the Krebs cycle nor be deposited. What are Keele and Neil in fact saying with these two doctrines? Cortisol excess raises the level of acetyl CoA which cannot be deposited and is therefore bound to find an outlet. The outcome is decided by the following factors:

1. The pathway of conversion to depot fat is blocked by cortisol and in fact the stream of FFA is going in the opposite direction.
2. The pathway into the Krebs cycle is blocked by impaired carbohydrate metabolism.
3. The one pathway left is the synthesis of cholesterol, which therefore increases.

I have described the biochemical processes leading to arteriosclerosis and increased cholesterol level, and they are entirely in agreement with *Samson's* two doctrines.

Carruthers: I realize now that these two doctrines explain how increased cholesterol level is a result of a biochemical derangement and must, therefore, be regulated biochemically.

Møller: Yes — that is the essential point. To quote *Samson* once more, "Cortisol promotes catabolism of proteins. Normally the breakdown of protein is counterbalanced by anabolic processes but excess of cortisol causes a negative nitrogen balance" (Keele and Neil 1982). In this case it is necessary to apply anabolic substances from the outside. Testosterone, which has a protein-sparing effect is the obvious choice. Testosterone restores the nitrogen balance and enhances dehydrogenase activity in the Krebs cycle and increases the concentration of 2,3-DPG (Ganong 1975, and others), thereby improving oxygen supply to the tissues.

I have pointed out that the same factors operate during a surgical operation in an acute form as in CVD. This is confirmed by countless publications. As mentioned in *Samson*, the organism is normally able to counterbalance these influences by endogenous anabolic processes and so restore homeostasis. Several authors suggest speeding up this balancing process by administering testosterone, which also has the effect of preventing postoperative thrombosis. *Samson* also mentions the administration of anabolic substances to postoperative patients.

Carruthers: You state that there is a relationship between catecholamines and pH. Could you clarify what you mean by this.

Møller: I have mentioned that an excess of catecholamines produces a rise in lactic acid level; and I cite the *Handbook of Physiology* (Table 3) showing that the higher the catecholamine output the lower the pH of the blood.

Carruthers: You mention thrombosis. I should like to hear more about this.

Møller: Thrombosis is said to have the same origin as infarction and is also a

very important factor in CVD. It can arise from anaerobic metabolism (formation of ADP), excess lactic acid, and release of clot-promoting factors caused by catecholamines in the circulation. As Weiner (1980) writes, catecholamines "given to experimental animals lead to damage to arterial walls and myocardium, so severe as to cause the appearance of necrotic areas, indistinguishable in the heart from myocardial infarcts." The vessels (whose cells participate in this anaerobic metabolism) are injured by catecholamines and release certain substances, such as ADP, which facilitate platelet aggregation (Anderson 1976; Gaarder 1961; Born 1964). Aerobic metabolism implies normal ATP and testosterone production, which counteracts platelet aggregation (Keele and Neil 1982). (The WHO Madrid report also states that testosterone inhibits platelet adhesiveness).

Carruthers: You talk about the WHO Madrid report. How does this report fit your theories?

Møller: It does fit indeed! This marvellous report from the WHO Symposium held in Madrid in 1972 is an inspiration for the physicians of today. The statements it contains are proved absolutely correct by my positive clinical results. Decreased fibrinolytic activity, increased cholesterol level, increased platelet adhesiveness, and increased fibrinogen are all factors in CVD; and the WHO recommends that they are all counteracted by testosterone, which causes a shift from anaerobic to aerobic metabolism.

Testosterone acts on all the interdependent and correlated factors underlying CVD. When testosterone decreases cholesterol level, a decrease in FFA and acetyl CoA follows. This again is connected with a normalization of carbohydrate metabolism and restoration of testosterone production, thus reducing protein breakdown by cortisol (the protein-sparing effect). Here is a remarkable effect. Testosterone administration leads to an increase in its *own* endogenous production, since this production depends on adequate oxygen supply, which is achieved by giving testosterone itself. The synthesis of testosterone from cholesterol relies on oxygen, as described by Stryer (1975, p.495): "Hydroxylation reactions play a very important role in the conversion of cholesterol to steroid hormones and bile salts. All of these hydroxylations require NADPH and $O_2$."

Carruthers: I think you have given yet another beautiful illustration of the wisdom of the body in its own natural self regulation. You also show that when homeostasis breaks down, the body is best helped by treatment with its own products such as testosterone.

It is also particularly satisfying to see the many ways in which the writing of Samson Wright, my first professor of physiology at the Middlesex Hospital in London, fit in so well with your revolutionary yet fundamental theories.

## Action Now on Circulatory Disease

by M. Carruthers

As a doctor involved in research and treatment of circulatory diseases for over 20 years I feel it my medical duty to make an urgent call for action now on circulatory disease.

I have already mentioned that I was immediately impressed by the truth and importance of Møller's message when I first heard him address the EOCCD

Exchanges of Views



meeting in the House of Lords in 1977, and I became a member of the organization from its earliest days. At other EOCCD meetings which I agreed to chair in London, Strasbourg, Bonn and other centers throughout Europe, I have consistently been made aware of the force of these arguments in favor of treating circulatory disease with anabolic steroid hormones.

Møller has collected a mountain of evidence, consisting of over a thousand references from the scientific literature, which is uniformly in favor of this approach. It documents with irresistible logic the mechanisms underlying circulatory disease and the benefits which can be obtained by treatment with anabolic steroids, and gives an authoritative scientific basis for it. This is a unique body of knowledge on the subject. We doctors must admit that, up to now, we have only been going from one wrong track to another.

Also having been fortunate enough to have had the opportunity over the last 8 years to spend several periods of up to a month in Møller's clinic in Copenhagen, I have seen hundreds of cases which have had dramatic benefit from this treatment. Consequently I can fully confirm the favorable reports on it given by visiting scientists from Great Britain. These leading doctors and research workers from London University and the top British research organisation, the Medical Research Council, came and witnessed the effects of hormonal treatment so convincingly demonstrated in Denmark. This clinic is truly the world leader in this field, and Danes should be proud of this achievement!

I therefore feel that the vital message of the this Danish based organization, the EOCCD, about the treatment of circulatory disease with anabolic steroids which it advocates in the saving of both life and limb, should be confirmed by a multidisciplinary committee of leading scientists. In this way it will become common knowledge, to the benefit of the patients. I fully agree with Møller when he says in his book: "I believe that the delay in the utilization of testosterone treatment for CVD has arisen from a failure by specialists in endocrinology, biochemistry, physiology, and cardiology to understand each other's points of view and therefore to coordinate their clinical efforts effectively. This is like four people starting to climb the various faces of a pyramid, unaware of each other's presence until they reach the apex. It is hoped that bringing specialists in these different disciplines together at summit meetings will help them discover the true nature of this disease, the cardiovascular specialist understanding the underlying lack of the anabolic factor and the other three grasping the way in which treatment with anabolic steroids can effectively countertact the metabolic disturbance which is the cause of CVD."

When this committee has spoken, it will be the duty of every health authority in the world to ensure that anabolic steroid treatment of circulatory disease is tried before the method of last resort, surgery.

I suggest that action needs to be taken here and now on implementing the only method of treatment which offers hope in preventing death and disability in thousands of patients each year from this modern epidemic of circulatory disease.

## Discussion with Gunde Egeskov Jensen

Gunde Egeskov Jensen is Lecturer and associated Professor of biochemistry and biology, University of Roskilde, Denmark.

Jensen: I have read the manuscript of your book *Cholesterol* with great interest and have noted in particular your co-operation with the man who has been such an inspiration to all biochemists and doctors — the late Sir Hans Krebs, Professor at Oxford University and Nobel Prize winner. Your correspondence with him begins with him saying that your clinical findings can stand by themselves, and he continues: "I take it you are anxious to see your clinical results and their interpretation underpinned by biochemical concepts, bearing in mind that all physiological and pathological events have some biochemical basis." I can see from the theories in your book that you have followed Professor Krebs' advice. Personally I would appreciate a deeper explanation of the relation between testosterone and cortisol, which appears to be very fundamental to the discussion in your book. This relationship is discussed in textbooks currently used in medical schools and universities. Could you give me a short description of how the action of these two hormones form the scientific basis of your theories?

Møller: Normally, cortisol and catecholamines convert protein to plasma glucose, which enters into the Krebs cycle under the influence of insulin, but the effect of overproduction of cortisol and catecholamines on the vascular system includes a reduction in cardiac output, an increase in energy expenditure for a given amount of cardiac work — in other words, anaerobic metabolism, impaired carbohydrate metabolism, and negative nitrogen balance. The cortisol excess leading to these metabolic changes can be counteracted by testosterone, normalizing both carbohydrate and protein metabolism. This action of anabolic testosterone and cortisol is transmitted to all the metabolic links in the organism, just as anabolic insulin affects all the metabolic disturbances in diabetes mellitus.

Jensen: It would be very interesting to hear more of this phenomenon.

Møller: An excess of stress hormone activates hormone-sensitive lipase leading to more plasma FFA than can be taken up by the citric acid cycle, in relation to oxaloacetic acid; because of the fact that acetyl CoA cannot accumulate, the result is an increase in the cholesterol level.

Jensen: How do you come to the result that the administration of testosterone in this case can alter the situation in the citric acid cycle?

Møller: Administration of testosterone activates post-heparin lipoprotein lipase, and consequently leads FFA into the citric acid cycle, reestablishing normal metabolism.

Jensen: You have given Sobel and Marmorston a prominent position. Does this article also confirm another link in the metabolic chain?

Møller: Yes. The positive effect of testosterone increases the ratio of hexosamine to collagen, thus increasing the oxygen supply to the tissues. Furthermore, in the case of anaerobic metabolism, administration of testosterone prevents a decrease in the activities of dehydrogenases of the Krebs cycle, not forgetting that testosterone increases 2,3-DPG. If the level of ATP with anaerobic metabolism sinks below half the normal production, the result is necrosis of the cell, with infarction or gangrene. Testosterone reestablishes aerobic metabolism, which means phosphorylation of ADP to ATP, healing of cardiac tissue after infarction, and the healing of gangrene.

Møller: The condensation of acetyl CoA to ketone bodies does not occur any more frequently with CVD patients than with healthy people. The etiology of diabetes mellitus is disturbance of insulin production resulting in impaired carbohydrate metabolism and *not* a lack of oxygen as in CVD. Diabetics can use ketone bodies for the production of energy up to the point of ketosis.

Jensen: We often hear warnings against a high level of cholesterol in our diet, which should have a negative effect on the circulation. What is your opinion of diet in connection with CVD?

Møller: According to textbooks, consumption of cholesterol should reduce the endogenous cholesterol production.

Jensen: You are opposed to decreasing cholesterol levels by clofibrate and similar substances. What are your reasons for this?

Møller: The metabolic cause of increased cholesterol levels should be corrected metabolically. I have repeatedly shown in my book that testosterone can normalize the metabolism, including the metabolism of cholesterol. Cholesterol is vital as the precursor of testosterone and cortisol. These two hormones keep each other in check in order to maintain our natural life processes, expressed by the ability to build up or break down protein. In spite of the impaired biological functions described by line a in Fig. 2, there are always very strong forces endeavoring to reestablish homeostasis by endogenous anabolic processes, as we know is the case with surgery. Stressful stimuli impose strain on the homeostatic mechanism of the body during every second of life. This response is important for survival. Clofibrate will destroy this mechanism.

Jensen: I agree. Also, in your book you write that you can help patients to regain homeostasis postsurgically by administration of testosterone.

Møller: Yes, but imagine a surgeon administrating clofibrate postsurgically in order to reduce an increased cholesterol level which is a normal link in the postsurgical process and a natural reaction to a stress stimulus.

Jensen: Can you give me, briefly, a good argument against double blind clinical trials in connection with CVD?

Møller: CVD cannot be cured. One can only improve the circulation, so there we lack the most important factor — curing of disease in a significant group. The majority of patients are in the higher age groups where one cannot separate the physiological and pathological parameters, and testosterone does not, of course, affect the physiological changes. What we have to stick to is whether testosterone affects the parameters causing CVD so that there is a significant improvement. This *has* been shown time and time again, for instance at the University of Copenhagen, where cholesterol levels of 83% of 300 patients were reduced. Also the Madrid Report of the WHO shows a significant decrease in cholesterol, and this is confirmed in other literature.

Jensen: You have written a book which I can highly recommend. I find it instructive and I am of the same opinion as my highly respected colleague, head of the Department of Biochemistry, University of Cambridge, Professor Richard Martin, who says that this scientific representation is so correct that it inspires to discussion and further biochemical research.

Møller: Thank you. Concerning the textbooks, though, I should like to go into detail and quote some passages which I feel will give you and Professor Martin an essential supplement:

Keele and Neil (1982):

Cortisol excess raises blood lipids and plasma cholesterol. This leads to atherosclerosis which is a feature of Cushings syndrome. (p.532)
The term Cushings Syndrome is applied to the clinical disorder which results from the exposure of body tissues to sustained supraphysiological blood levels of corticosteroids, either endogenous in origin or iatrogenically produced. (p.535)
Normally, breakdown of protein is counterbalanced by anabolic processes but excess of cortisol causes a negative nitrogen balance. (p.532)

Ganong (1975):

Following administration of steroids such as testosterone, nitrogen intake exceeds excretion and nitrogen balance is positive. (p.220)

Consequently endogenous or iatrogenically produced cortisol leads to a negative nitrogen balance and CVD. Here in my clinic we have, by titration, been able to see how much testosterone was necessary to normalize impaired carbohydrate metabolism, cholesterol and postheparin lipoprotein lipase, that is to say, how many milligrams can neutralize so and so many milligrams of cortisol. There are plenty of examples of this in the literature.

Jensen: Yes I am aware of that. For instance Brøchner-Mortensen et al. (1959):

1. The nitrogen, calcium, and phosphorus balance has been followed in five patients with chronic rheumatoid arthritis, with the aim of investigating whether the new 19-nor-steroids Nilevar and Durabolin are capable of inhibiting the excess excretion of nitrogen and calcium which develops as an undesirable side-effect in prednisone treatment.
2. The investigation shows convincingly that the catabolic action of prednisone can be inhibited, if an anabolic 19-nor-steroid is administered concurrently.
3. The action of 19-nor-steroids on the calcium balance is less obvious, particularly in the case of bedridden patients. In one single case, however, there was a convincing effect from 19-nor-steroid, both when administered alone and in combination with prednisone.
4. In two out of the four women there was a vaguely increased hirsutism of the upper lip, but apart from this there was no virilization which necessitated withdrawal of therapy. Nilevar, however, in contrast to Durabolin, showed a very strong progestational effect, which in the authors' opinion reduces its practical clinical value as an anabolic compound.
5. The action of injected Durabolin is considerably stronger and persists much longer than the action of Nilevar administered perorally.
6. In the limited material in this study, neither Nilevar nor Durabolin appears to inhibit the beneficial action of prednisone on the articular symptomps.
7. The investigation appears to demonstrate that the administration of 19-nor-steroid can counteract certain undesirable metabolic effects in the long term treatment with prednisone. However, the practical significance of this combination therapy cannot be evaluated until it has been employed in larger clinical series. When such investigations are undertaken due attention should be paid to the fact, that almost nothing is known at the present time about possible hazards in long-term 19-nor-steroid therapy.

Jensen: According to your theories this publication should participate in the proof that testosterone must be used in the treatment of CVD.

Møller: Quite right. And last but not least I can refer to the clinical results of the treatment.

Jensen: Yes, we are all familiar with these, and I repeat the words of the late Professor Krebs: "Your clinical findings can stand by themselves."

# Epilogue

For many years I have been engaged in medical science and I feel that I more or less share the opinion of Thomas Jefferson:

> Our natural philosophy is in a very infantile state .... Surgery is well advanced; but prodigiously short of what may be. The state of medicine is worse than that of total ignorance. Could we divest ourselves of everything we suppose we know in it, we should start from a higher ground and with fairer prospects. From Hippocrates to Brown we have had nothing but a succession of hypothetical systems each having it's day of vogue, like the fashions and fancies of caps and gowns, and yielding in turn to the next caprice. Yet the human frame, which is to be the subject of suffering and torture under these learned modes, does not change. We have a few medicines, as the bark, opium, mercury, which in a few well defined diseases are of unquestionable virtue; but the residuary list of the materia medica, long as it is, contains but the charlataneries of the art; and of the diseases of doubtful form, physicians have ever had a false knowledge, worse than ignorance. (Quoted in Oppenheimer 1966)

It is also my experience that the colleagues in power or the majority decide what is science and what is not. Galileo would surely turn in his grave if he knew that in this regard no progress had been made since his time. For years it was "in" that butter could cause and margarine cure CVD. The cholesterol level had to be lowered by any means regardless of the fatality of the treatment. Physical exercise was propagated to the extreme, endangering people's lives. Lifelong antihypertensive treatment to reduce suffering apparently often reduced life instead.

I have always claimed that physical activity is the best means of improving the circulation when the patient is in stage 1 (claudication). Even at this stage, however, the case may be so severe that administration of testosterone is required. Every student nurse knows that a bedridden patient develops muscle atrophy due to lack of physical activity. Administration of testosterone to such a patient has only a minor effect. To fully benefit from testosterone treatment it must be combined with physical activity (and with ample protein in the diet). It is a fact acknowledged today in university textbooks and other serious publications that physical activity produces testosterone, which promotes an increase in muscle mass. This again leads to a spontaneous and unconscious increase in physical activity, and the cycle continues. By using physical activity as treatment we doctors are in reality "prescribing" testosterone from the patients' endogenous reserves. In other words, exercise and administration of testosterone have the same effect on the circulation i.e., decreased cholesterol level, improvement of carbohydrate metabolism, normalization of lipoprotein lipase and hormone sensitive lipase — in every respect positive effects on all the parameters in the cogwheel system.

Times are changing and we are living in a new era. The world is very different from that of a few years ago and this also applies to the medical profession where the changes are not necessarily for the better. Physicians of my generation were brought up to consider first and foremost the welfare of the patients and definitely not to experiment with their health. Anyhow, doctors should by no means be motivated by personal interests or vanity. I have always kept my theories and

treatment strictly within the range of solid scientific facts which we know for certain to improve the circulation and I have refused to become involved with, or seduced by the previously mentioned colleagues with their haphazard ideas and their thirst for power. If we were able to literally *see* the whole process of cardiac function and its improvement after testosterone administration, we would never dream of performing operations such as heart transplantations. The immune reactions involved in postsurgical treatment of these patients will inevitably lead to impairment of the whole circulation. As for myself, I cannot literally observe the heart in action. I *can*, though, see the results of testosterone administration in the form of healed gangrene — which is in fact "infarction" of the foot. In Europe we have a medical history of which we should not be ashamed but of which we can be proud. In this regard I can mention several scientists with special connection to my line of work. From my own country, for instance, Teilum and Rovsing, and from Germany Butenandt and Virchow. It is beyond all doubt that we have received the results of much valuable scientific research from the U.S.A., but it would do no harm if we could be just as critical and sceptical as the Americans themselves are about their own methods. It seems to me that we here in Europe, in many cases, have sold our birthright for a mess of pottage.

A case in point was the use of clofibrate. I am once again struck by the paradox that such a substance has been used to lower plasma cholesterol. Clofibrate has a significant effect on the cholesterol balance in the metabolism, as more cholesterol is excreted fecally than the organism is able to synthesize itself. In other words, the result is a negative cholesterol balance, which can lead to impotence and impaired cardiac function, resulting for instance in angina pectoris and other signs of serious cardiovascular disease such as claudication. (As far as impotence is concerned, this is a confirmation of my theory. The cholesterol is wasted by going down the drain instead of building up testosterone.) It is totally incomprehensible to me how such a substance can be used by serious practitioners in medicine, who inflict CVD on their patients instead of curing it.

Another example of a treatment which addresses a single parameter without due consideration for the others is the use of hypoglycemic agents in maturity-onset diabetes, discussed in the chapter on diabetic states. These are used to counteract increased plasma glucose in the same blinkered way as clofibrate is used against cholesterol, and exactly the same result is achieved: the reduction in blood glucose caused by these agents simply leads to CVD.

I have presented a great deal of evidence in favor of treating patients with testosterone, but in the final analysis what better evidence is there of the beneficial effects of testosterone on the circulation than the fact that gangrene is healed. This is the living proof of an improved circulation, better than any amount of statistics and clinical trials — trials which are in any case impossible to carry out with this type of disease. We must stick to the parameters and the limitations these impose. As Professor Richard Martin of the Cambridge Department of Biochemistry has written to me in a personal communication, "it is difficult to produce relevant statistics on the patients' general health when dealing with a degenerative disease." I would go further, and say that it is impossible. Those who demand this type of evidence have simply failed to understand the nature of cardiovascular disease.

To sum up: the main contents of this book concern fundamental catabolic and anabolic forces in the metabolism expressed via chemical mediators such as cortisol and testosterone.

*Catabolism.* The negative influence of cortisol on protein metabolism involves deamination of the amino acids from which glycogen is formed. The negative effect of catabolism on actin and myosin involves decreased stroke volume, which can be seen from ischemic signs on the ECG. Catabolism also means:

Decreased enzyme activity in Krebs cycle
Decreased fibrinolytic activity
Decreased ATP-ADP ratio, leading to increased platelet adhesiveness
Activation of the hormone-sensitive lipase by *cortisol* ("Cortisol excess raises blood lipids and plasma cholesterol level. This lead to arteriosclerosis." — Keele and Neil, 1982).

Impairment of the carbohydrate metabolism, leading to an increase in acetyl CoA due to a lack of oxaloacetic acid. Acetyl CoA is then unable to enter into the Krebs cycle, and the result is *hypercholesterolemia.*

*Anabolism.* Testosterone builds up protein from amino acids, decreasing glycogen formation. The positive effect of testosterone on actin and myosin involves increased stroke volume, evident from the normalization of ischemic signs on the ECG.

Testosterone also means:

Increased enzyme activity in Krebs cycle
Increased fibrinolytic activity
Increased ATP-ADP ratio and decreased platelet adhesiveness
Increased lipoprotein lipase activity and improved carbohydrate metabolism

The triglycerides are now metabolized and *cholesterol level is lowered.* This prevents the process described by Keele and Neil (1961) as: "Cholesterol is synthesized from active acetate units in lieu of their conversion to fatty acids and leads to the rapid development of arteriosclerosis."

When the two opposing forces of catabolism and anabolism are balanced we have homeostasis. Where there is imbalance, the catabolic forces are predominant, that is, all factors pull in the same direction. Testosterone reverses the process, pulling all the parameters in the opposite, anabolic direction until homeostasis is achieved (cogwheel).

# Publications Dealing with the Effect of Testosterone on the Parameters of CVD

1. Breier,Ch., Drexel,H., Lisch,H-J., Mühlberger,V., Herold,M., Knapp,E., Braunsteiner,H.
   Essential role of post-heparin lipoprotein lipase activity and of plasma testosterone in coronary artery disease.
   Lancet, June 1, 1242-1244, 1985.

Summary: 89 consecutive men for whom coronary angiography was requested because of suspected coronary artery disease were investigated with respect to plasma lipids, lipoproteins, post-heparin lipoprotein lipase (LPL). and some hormones that influence LPL. The severity of coronary-artery disease was expressed by the coronary score (CS). Coronary artery-disease correlated with total plasma cholesterol, low-density lipoproteins, high-density lipoprotein cholesterol (HDL-chol), and HDL2. In addition, there was a strong negative correlation ($r = -0.479$, $p<0.001$) between CS and LPL, as well as positive correlations between CS and plasma triglycerides ($p<0.01$) and very low-density lipoproteins (VLDL, $p<0.01$). The impairment of LPL activity correlated with increased VLDL and decreased HDL-chol. The extent of coronary-artery disease is thus strongly influenced by an LPL deficit. LPL activity correlated with plasma testosterone, and there is evidence that low plasma testosterone may be partly responsible for the low LPL and HDL-chol.

2. Haug,A., Høstmark,A.T., Spydevold, Ø.
   Plasma Lipoprotein Responses to Castration and Androgen Substitution in Rats.
   Metabolism, 33, 5, 1984.

To elucidate plasma testosterone/lipoprotein relationships in a controlled animal experiment, whole-plasma lipid concentration and amount of lipoprotein components in five density classes were determined in three groups of rats: normal control rats, short-term castrated rats, and rats treated with testosterone propionate after castration. Compared to control rats, whole-plasma total cholesterol, free cholesterol (FC), cholesteryl-ester (CE), and phospholipids (PL) rose in castrated rats but were normalized in rats receiving androgen substitution. There were no group differences in whole-plasma triacylglycerol concentration. The levels of protein, FC, and CE in LDL ($d = 1.006$ to $1.063$ g/mL) and HDL2b ($d = 1.063$ to $1.100$ g/mL) of castrated rats were appreciably higher than in LDL and HDL2b of control rats. In androgen-substituted rats the level of LDL and HDL2b protein, FC, CE, and PL were all reduced to normal or subnormal levels. The esterified fraction of cholesterol in whole plasmawas increased by androgen treatment. There were no significant group differences in VLDL ($d < 1.006$ g/mL), HDL2b ($d = 1.100$ to $1.125$ g/mL) or in HDL3 ($d = 1.125$ to $1.210$ g/mL). The results suggest that short-term castration of rats is followed by hyperlipoproteinemia due to lack of testoterone and that the lipoprotein changes mainly reside in LDL and the less-dense type of HDL.

3. Vaismann,I., Cantisano,L., Granato,P.O.
   Über die blutcholesterolsenkende Wirkung androgener Hormone.
   Ärzliche Forschung, 11, 1960.

The authors investigate the relationship between androgens and thyroid hormones. They found a significant decrease in cholesterol levels through the use of androgens. For that reason the use of androgens in hypercholesterolemia is being recommended.

4. Kumada,T., Abiko,Y.
   Enhancement of Fibrinolytic and Trombolytic Potential in the Rat by Treatment with an Anabolic Steroid, Furazabol.
   Trombos. Haemostas. (Stuttg.). 36, 1976.

The effect of long-term ingestion of an anabolic steroid, furazabol, was studied on coagulo-fibrinolytic systems in the rat.

During the administration of furazabol at the daily dose of 0.04, 0.2 or 1 mg/rat for 3 monts, the most remarkable changes were increase in the plasminogen activator activity in the blood and the lung tissue and decrease in plasma fibrinogen level as well as decrease in plasma cholesterol. It was a very important finding that in most of the rats the furazabol treatment was effective in reducing susceptibility to lactic acidosis-induced pulmonary thrombosis.

5. Andersen,P., Norman,N., Hjermann,L.
Reduced Fibrinolytic Capacity Associated with Low Ratio of Serum Testosterone to Oestradiol in Healthy Coronary High-risk Men.
Scand. J. Haematol. – Suppl. 30, 39, 53-57, 1983.

In a study of 42 healthy, middle-aged men with high risk of coronary heart disease (CHD), we found a highly significant correlation between low ratio of serum testosterone to oestradiol and delayed clot lysis after venous stasis as measured with the euglobulin clot lysis time (ECLT). The upper normal limit of ECLT was set at 60 min. Half of the examined specimen, i.e. from 21 individuals, lysed as normal; 4 specimen lysed between 60 and 90 min, whereas the remaining 17 specimen did not lyse within 2 hours. Sixteen of these 17 individuals with the most defective fibrinolytic capacity belonged to the group of individuals with the lowest ratio of serum testosterone to oestradiol. The association was highly significant ($p < 0.001$). In comparison, the correlation between serum triglyceride concentration and the rartio of serum testosterone to oestradiol was significant at the 2% level, whereas serum cholesterol and this ratio were not associated. The significance of the findings remains obscure, but may be important for the incidence of CHD in men.

6. Davidson,J.F., Lochhead,M., McDonald,G.A., and McNicol,G.P.
Fibrinolytic Enhancement by Stanozolol: A Double Blind Trial
British Journal of Heamatology, 22, 543, 1972.

Summary. Thirty-four men with ischaemic heart disease were given 10 mg stanozolol per day, 10 mg stanozolol plus 100 mg phenformin per day, or a palcebo for 12 mth, in a double blind randomized study. A panel of fibrinolytic and coagulation tests was performed at monthly intervals. Throughout the study the group on active treatment showed significant enhancement of plasma fibrinolytic activity compared with their base-line values, and compared with the palcebo group. No significant difference was found in the enhancement of fibrinolysis which was produced by either active treatment regimens, and it is concluded that 10 mg stanozolol daily is as effective as 10 mg stanozolol plus 100 mg phenformin daily in increasing plasma fibrinolytic activity in men with ischaemic heart disease.

7. Gorokhovski,B.I., Kitaeva,I.T.
The Use of Anabolic Hormones in Myocardial Infarction (in Russian). Klin. Med. (Mosk). 48, 29-34. 1970.

Summary. In 70 patients with transmural myocardial infarction, along with rutine treatment, the authors administerred 20 mg of nerobol daily for two months. As control served 70 patients with transmural myocardial infarction who did not receive nerobol. Under the effect of nerobol treatment there was an improvement of the general state of the patients. In the latter, in comparison with patients not receiving nerobol, there were lesser seizures of angina pectoris and cardiovascular insufficiency, there occured an early positive ECG dynamics, more rarely were there cardiac rhythm and conduction disorders, and cardiac aneurysm, the myocardial contractile activity improved.

8. Bardin,E.V., Razumovich,A.N., Dubina,T.L., Kamentseva,V.I., Karput,S.N. Lapotko,Yu.N., Lastovskaia,T.G., Nikishkin,I.A., Novikova, I.A., and Khmara,N.F.
The Effect of Testosterone Propionate on Some Indicators of Energetic Metabolism in the Intact Zone in Experimental Myocardial Infarction.
Cor Vasa 15 (3), 209-221, 1973

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Summary. The effect of testosterone propoinate (TP) on the state of energetic metabolism in the left ventricular intact zone was studied in rabbits with experimental myocardial infarction (EMI) produced by coronary artery ligation, and in normal male rabbits. Four groups of animals were involved, as follows: (a) experimental animals with EMI (11) receiving TP dosed 4 mg/kg daily for 10 consecutive days following surgery; (b) control group of untreated animals with EMI (11); (c) experimental group of intact animals (11) receiving TP dosed as in the group (a) with EMI; (d) second control group – untreated normal rabbits (10). In the intact myocardial zone, the following checkings were made: oxygen uptake; levels of adenosine triphosphate (ATP), creatine phosphate (CP), inorganic phosphate (Pi), phospholipids, cholesterol, SH groups, total protein, activities of flavoproteins, cytochrome oxidase, ATPase, lactate dehydrogenase, and aminotransferases.

In rabbits with EMI there were observed: decrease in ATP and CP levels, decrease in activities of flavoproteins and cytochrome oxidase, accelerated $O_2$ uptake, and increased Pi level. In normal rabbits the administration of TP led to an augmentation of SH groups and an activation of some links in the respiratory cycle: the oxidation rates of succinate and alpha-ketogluterate accelerated, and the cytochrome oxidase activity increased. The administration of TP to anaimals with EMI stimulated the activity of flavin enzymes and transamination reactions, raised the CP (and to a lesser extent, also the ATP) levels, enhanced the SH groups and the phospholipid levels, normalized the Pi level, and reduced the cholesterol level.

9. Jaffe,M.D.
Effect of Testosterone Cypionate on Postexercise ST Segment Depression.
British Heart Journal, 39, 1217-1222, 1977.

A randomised double blind study was carried out with 50 men who had ST segment depression of 0.1 mV or more after a modified two-step exercise test. Rate and duration of exercise were the same for the last of each subject's several pretreatment tests as for his tests after 4 and 8 weeks of treatment with placebo or testosterone cypionate, 200 mg, intramuscularly weekly. The sum of ST segment depession in leads II, V4, V5, and V6 taken immediately, and 2, 4, and 6 minutes after exercise did not changes significantly after 4 or 8 weeks of placebo treatment, but did decrease by 32 per cent ($P < 0.0001$) and 51 per cent ($P < 0.0001$) after 4 and 8 weeks, respectively, of testosterone cypionate treatment. The mechanism by which testosterone cypionate treatment results in lessened postexercise ST segment depression is not established.

10. Kalliomäki,J.L., Seppälä
Norandrostenolone Decanoate as a Cardiac Anabolizer Studied by Means of Electrocardiographic Changes.
Cardiologia 43, 124-128, 1963.

Summary: 22 cardiosclerotic patients have been treated with norandrostenolone decanoate during periods of 1-5 months. In 12 cases a decrease of electrocardiographic abnormalities was observed, in 2 cases these abnormalities increased during the treatment and in 8 cases no change in the electrocardiographic findings was seen during the administration of this anabolic steroid.

11. Gudbjarnason,S., Ravens,K.G., Mathes,P.
Metabolic Changes in Infarcted and Non-infarcted Myocardium During the Postinfarction Period.
In: Bajusz,E., Rona,G. (eds) Myocardiology.
Urban and Schwarzenberg, Müchen: University Park Press, Baltimore, 439-446 (Recent advances in studies on cardiac structure and metabolism. Vol.1). 1972.

Following acute myocardial infarction in dogs, there is a significant, reversible diminution in tissue levels of ATP, creatine phosphate, and norepinephrine in noninfarcted heart muscle. The diminution in ATP and CP levels of the noninfarcted muscle is accompanied by a significant impairment in myocardial function as reflected in the decrease in rate of pressure rise (dp/dt) or stroke work. Treatment with anabolic steroids significantly increases the ATP level of noninfarcted muscle, whereas a protein-free diet results in a significant diminution in myocardial ATP level and increased mortality. Scar formation in cardiac muscle is markedly reduced by 26%. These results suggest that diet and anabolic hormones may play an important role during tissue repair and muscle recovery, following acute myocardial infarction.

12. Parker,J.P., Bierne,G.J., Desai,J.N., Raich,P.C., Shahidi,N.T.
Androgen-induced Increase in Red-cell 2,3-Diphosphoglycerate.
The New England Journal of Medicine, Aug. 2, 1972.

Abstract: The administration of testosterone enanthate to six patients with chronic renal failure on biweekly hemodialysis increased erythrocyte 2,3-diphosphoglycerate (2,3-DPG) in all patients. Whereas the value was 5670 ± 550 (mean ± S.E.) nmoles per milliliter of red blood cells before treatment, it was 9097 ± 760 after 12 weeks of androgen therapy. This increase was statistically significant (p less than 0.01). None of a group of seven similarly affected patients who did not receive androgens and were followed within the same period showed any increase in red-cell 2,3-DPG. The shift in oxygen equilibrium curve to the right that results from testosterone enanthate should greatly enhance the unloading of oxygen to the tissues.

13. Fuller,J.H., Shipley,M.J., Rose,G., Jarrett,R.J., Keen,H.
Coronary-heart-disease Risk and Impaired Glucose Tolerance.
Lancet I, 1373-1376, 1980.

Summary: In the Whitehall Study of 18403 male civil servants aged 40-64 years, 7 1/2-year coronary-heart-disease (CHD) mortality has been examined in relation to blood-sugar concentration 2 h after a 50 g oral glucose load. CHD mortality was approximately doubled for subjects with impaired glucose tolerance (IGT), defined as a blood-sugar above the 95th centile (≥96 mg/dl). There was no trend of CHD mortality with blood-sugar below the 95th centile. Within the IGT group, age, systolic blood-pressure, and ECG abnormality (Whitehall criteria) were significantly predictive of subsequent CHD mortality. These findings are relevant to discussion on the criteria for diabetes which include the definition of an IGT category with increased risk of large-vessel disease, but without the high risk of small-vessel disease as occurs in diabetes mellitus.

14. Isacson,S.
Effect of Prednisolone on the Coagulation and Fibrinolytic Systems.
Scan. J. Haemat. 7, 212-16, 1970.

In an extensive investigation of the coagulation and fibrinolytic systems in 12 healthy volunteers it was found that adminstration of 20 mg prednisolone per day for 11 days increased the AHF-factor and tended to induce a hypofibrinolytic condition. Histochemical analysis of biopsies of superficial veins revealed that the plasminogen activator content of the specimens was decreased and thereby showed for the first time that a drug can interact with the plasminogen activator content in the vessel walls.

15. Lesser,M.A.
Testosterone Propionate Therapy in One Hundred Cases of Angina Pectoris.
J. Clin. Endocrinol. 6, 549-557, 1946.

Summary: One hundred patients with angina pectoris, 92 men and eight women, ranging from 34 to 77 years in age, have been treated during the last five years with testosterone propionate. Ninety-one per cent improved for periods ranging from 2 to 34 months.

In the majority of the patients 25 mg of the hormone was administered on the average of twice a week for the first two weeks, followed by weekly 25 mg injections, with an average of 12 injections in the whole series.

No appreciable improvement was noted followed control injections of plain sesame oil, although the same patients responded when placed on testosterone propionate therapy.

With appropriate dosage in the cases studied, no untoward effects were observed.

Four patients were studied by means of exercise-tolerance tests before and during the course of treatment to obtained objective measurements of their improvement. In each of these patients the amount of exercise which could be tolerated before the development of an anginal attack was markedly increased under testosterone therapy, and the severity of attacks, as measured by the duration of the pain, was correspondingly diminished. In each case, subjective improvement was reported before objective changes could be demonstrated by the test employed.

The summary of this larger series of cases of angina pectoris treated with testosterone propionate confirms the results previously reported. [This is a case of a clinical trial where testosterone is compared with placebo treatment].

16. Teilum,G.
Om Hormonal Cholesterinæmi. (With an English summary).
Ejnar Munksgaards Forlag, København, 1940.

I have come across this very interesting book by Gunnar Teilum from 1940. A few extracts from it show how science already at that time looked upon the subject "cholesterol."

Bürger and Beumer (1913): Dietary cholesterol plays a very inferior role in plasma cholesterol level.

Ssokoloff (1923) found no increase in cholesterol level in healthy persons who were given 3 g cholesterol three times daily for three days.

Thannhauser (1929) believes that there is no connection between hypercholesterolemia and arteriosclerosis.

Eisler (1930): A 7-year-old girl had taken vitamin D without supervision for several years. X-ray showed arteriosclerotic changes extending right out into the periphery of the arteries. This is of special interest in Denmark since physicians who seem to have some authority recommended vitamin D as a prophylactic measure. The result was that vitamin D, which is vital for children, were sold out within a few days after this recommendation.

McCullagh (1934) transplanted testis from a 45-year-old man to a 75-year-old, whose cholesterol level fell from 215 mg% to 160 mg% (see also Rovsing mentioned in the Foreword).

A diagram in the book shows how after castration the level of cholesterol gradually increases from a mean value of 170 mg% to 250 mg% after 6 years.

It is amazing to me to hold this book in my hand and realize what was known in 1940 about the relationship between testosterone and cholesterol and to then compare this valuable basic research with how this problem is maltreated nowadays. Why and for what purpose has the work of these renouned scientists been ignored?

**References:**

Bürger,M., Beumer,H.
H. Arch. f. exp. Path. u. Pharm. 71. 311. 1913.

Eisler,F.
Klin. Wochenschr. 9. Jahrg. II. 1846. 1930.

Mc.Gallach,E.P., Renshaw,J.F.
J.A.M.A. 103. 1140. 1934.

Ssokoloff,N.A.
Virch. Arch. 245. 203. 1923.

Thannhauser,S.J.
Stoffwechsel und Stoffwechselkrankheiten.
München, 1929. (S. 493. Cholesterinstoffwechsel).

# References


Aakwaag,A., Bentdal,O., Quigstad,K., Walstad,P., Ronningen,H., Fonnum,F.
Testosterone and Testosterone-Binding Globulin (TeBG) in Young Men During Prolonged Stress.
Int. J. Androl. 1. 22-31. 1978.

Allison,S.P., Prowse,K., Chamberlain,M.J.
Failure of Insulin Response to Glucose Load During Operation and After Myocardial Infarction.
Lancet I. 292. 478-481. 1967.

Allison,S.P., Tomlin,P.J., Chamberlain, M.J.
Some Effects of Anaesthesia and Surgery on Carbohydrate and Fat Metabolism.
Br. J. Anaesth. 41. 588-593. 1969.

Anderson,W.A.D., Scotti,T.M.
Synopsis of Pathology. 9th edn.
The C.V.Mosby Company. Saint Louis. 1976.

Atkinson,J.
News from American Hearts. 56 scientific sessions.
Academy Newsletter. 89. 222-227. 1983.

Bardin,W.
Hormonal Control of Testicular Function.
In: Brobeck,J.R. (ed) "Best and Taylor's Physiological Basis of Medical Practice". 10th edn.
Williams and Wilkins, Baltimore/London. 1979.

Blasius,R., Käfer,K., Seitz,W.
Untersuchungen Über die Wirkung von Testosteron auf die Contractilen Strukturproteine des Herzens.
Klinische Wochenschrift. 34.324-326. 1956.

Born,G.V.R., Cross,M.J.
Effects of Inorganic Ions and of Plasma Proteins on the Aggregation of Blood Platelets by Adenosine Diphosphate.
J. Physiol. 170. 397-414. 1964.

Boyd,W.
Pathology for the Physician. 7th edn.
Lea and Febiger. Philadelphia. 1965.

Breier,C., Mülberger,V., Drexel,H., Herold,M., Lisch,H.-J., Knapp,E., Braunsteiner,H.
Essential Role of Post-heparin Lipoprotein Lipase Activity and of Plasma Testosterone in Coronary Artery Disease.
Lancet. June 1. 1242-1244. 1985.

Butenandt,A.
Über die Physiologie und Chemie der Sexualhormone.
Verh. Dtsch. Ges. Inn. Med. 46. 276-294. 1934.

Butenandt,A., Tscherning,K.
Über Adrosteron V. Androstandiol, ein physiologisch hoch aktives Reduktionsprodukt des Androsterons.
Hoppe-Seyler's Z.Physiol. Chemie 234. 224-234. 1935.

Butenandt,A., Hanisch,G.
Über Testosteron. Umwandlung des Dehydro-androsterons in Androstendiol und Testosteron: ein Weg zur Darstellung des Testosterons aus Cholesterin.
Hoppe-Seyler's Z. Physiol. Chemie 237. 714-723. 1935.

Carruthers,M.
Danish Experiences in the Treatment of Advanced Circulatory Disease with Anabolic Steroids.
Bullitin. E.O.C.C.D. 6. 1980.

Damber,J.E, Janson,P.O.
The Effects of LH Adrenaline and Noradrenaline on Testicular Blood Flow and Plasma Testosterone Concentrations in Anesthetized Rats.
Acta Endocrinologica. 88. 390-396. 1978.

Davidson,J.F., Lochhead,M., McDonald,G.A., McNicol,G.P.
Fibrinolytic Enhancement by Stanozolol: A Double Blind Trial.
British Journal Haematology. 22. 543-559. 1972.

Doyle,A.E.
What is Ageing?
Medicographia. 5. 1983.

Ehrlich,J.C., Shinohara,Y.
Low Incidence of Coronary Thrombosis in Myocardial Infarction.
Archives of Pathology. 78. 432-444. 1964.

Einfeldt,H.
Zur Therapie von Durchblutungsstörungen mit Sexualhormonen und deren Derivaten.
Therapiewoche 26. 4111-4137. 1976.

Franke,H.
The Heart in Age.
Ciba Rev. 3. 1981.

Fuller,J.H., Shiply,M.J., Rose,G., Jarrett,R.J., Keen,H.
Coronary Heart Disease Risk and Impaired Glucose Tolerance.
Lancet I. 1973-1976. 1980.

Gaarder,A., Jonsen,J., Laland,S., Hellem,A., Owren,P.A.
Adenosine Diphosphate in Red Cells as a Factor in the Adhesiveness in Human Blood Platelets.
Nature (London). 192. 531-532. 1961.

Ganong,W.F. (ed)
Review of Medical Physiology, 7th edn.
Lange Medical Publications. Los Altos. 1975.

Gilman,A.G., Goodman,L.S., Gilman,A. (eds)
Goodman and Gilman's The Pharmacological Basis of Therapeutics. 6th edn.
McMillan. New York. 1980.

Green,J.H.
An Introduction to Human Physiology, 4th edn.
Oxford University Press, Oxford. 1976.

Goldstein,S.
Human genetic disorders that feature premature onset and accelerated progression of biological ageing.
In: Schneider,E.L. (ed), The Genetics of Ageing.
Plenum. New York. 1978.

Griffiths,J., Leung,F.
The sequential estimation of plasma catecholamines and whole blood histamine in myocardial infarction.
Am. Heart J. 82. 171-179. 1971.

Gudbjarnason,S., Ravens,K.G., Mathes,P.
Metabolic Changes in Infarcted and Non-Infarcted Myocardium During the Postinfarction Period.
In: Bajusz,E., Rona,G. (eds) Myocardiology.
Urban and Schwarzenberg. München. University Park Press. Baltimore. 439-446.
(Recent advances in studies on cardiac structure and metabolism. Vol 1). 1972.

Hamilton,J.B., Hubert,G.
Photographic Nature of Tanning of the Human Skin as Shown by Studies of Male Hormone Therapy.
Science. 18. 2290. 1938.

Hammer,F.
Zur Behandlung von Altersherzerkrankungen mit anabolen Steroiden.
Die Medizinische Welt. Nr. 51. 1966.

Janda,J., Mrhová,O., Urbanová,D., Linhart,J.
The Effect of Anabolic Hormone 19-Nortestosterone Propionate on the Metabolism of Straited Muscle During Experimental Ischaemia.
Pflügers Archiv. 361. 159-163. 1976.

Keele,C.A., Neil,E.
Samson Wright's Applied Physiology, 11th and 13th edn.
Oxford University Press, Oxford. 1961, 1982.

Klensch,H.
Der basale Noradrenalinspiegel im peripheren venösen Blut des Menschen.
Arch.Ges.Physiol. 290. 218-224. 1966.

Kochakian,C.D., Murlin,J.R.
J. Nutrition. 10. 437. 1935.

Kowalewski,K.
Activity of Malic Dehydrogenase and DPN-Cytochrome-C-Reductase of Liver Mitochondria in Rats Treated with Cortisone and with an Anabolic Androgen.
Proc. Soc. Exp. Biol. and Med., v113. 1963.

Landsforeningen til bekœmpelse af Kredsløbssygdomme. Symposium sur les maladies vasculaires. Strasbourg, June 20-21. 1975.

Larner,J.
Insulin and Oral Hyperglycemic Drugs; Glucagon.
In: Gilman,A.G., Goodman,L.S., Gilman,A. (eds). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 6th edn.
McMillan. New York. 1980.

Lehninger,A.L.
Principles of Biochemistry.
Worth Publishers Inc., New York. 1982.

Møller,J.
The Concentrations of Cholesterol and Tesosterone in the Blood of Male Patients with Circulatory Diseases. Bullitin E.O.C.C.D. 1, 1-4. 1977.

Møller,J.
Cholmondeley Room, House of Lords.
Bullitin. E.O.C.C.D. 2. 1977.

Møller,J., Einfeldt,H.
Testosterone Treatment of Cardiovascular Disesases
Springer Verlag, Berlin, Heidelberg, New York, Tokio. 1984.

Myerson,A., Neustadt,R.
Influence of Ultraviolet Irradiation Upon Excertion of Sex Hormones in the Male.
Endocrinology 25. 7. 1939.

Nahas,G.G., Zagury,D., Milhaud,A., Manger,W.M., Pappas,G.D.
Acidemia and catecholamine output of the isolated canine adrenal gland.
Am. J. Physiol. 213. 1186-1192. 1967.

Okamoto,R., Hatani,M., Tsukitani,M., Suehiro,A.
The Effect of Oxygen on the Development of Atherosclerosis in WHHL Rabbits.
Atherosclerosis. 47. 47-53. 1983.

Oppenheimer,J.R.
Science and Common Understanding.
Touchstone, New York. 1966.

Oyama,T., Aoki,N., Kudo,T.
Effect of Halothane Anesthesia and of Surgery on Plasma Testosterone Levels in Man.
Anesth. Analg. 51/1. 130-133. 1972.

Parker,J.P., Bierne,G.J., Desai,J.N., Raich,P.C., Shahidi,N.T.
Androgen-Induced Increase In Red-Cell 2,3-Diphosphoglycerate.
N. Engl. J. Med. 287. 381-383. 1972.

Phillips,G.B., Castelli,W.P., Abbott,R.D., McNamara,P.M.
Association of Hyperestrogenemia and Coronary Heart Disease in Men in the Framingham Cohort.
The American Journal of Medicine. 74. 863-869. 1983.

Raab,W.
Neorohormonalbedingte Herzkrankheiten. Pathogenese und Therapie.
Arch. Kreislaufforsch. 15. 39-63. 1949.

Raab,W.
Pathological Fundamentals of the Origin and Prevention of Degenerative Heart Disease.
Ann. N.Y. Acad. Sci. 156. 281-284. 1969.

Raab,W.
Why "Myocardiology".
In: Bajusz,E., Rona,G. (eds) Myocardiology. Recent Advances in Studies on Cardiac Structure and Metabolism. Vol 1. University Park Press. Baltimore. Urban and Schwarzenberg. Munich. 1972 (a).

Raab,W.
Cardiotoxic Effects of Emotional, Socioeconomic, and Environmental Stress.
In: Bajusz,E., Rona,G. (eds) Myocardiology. Recent Advances in Studies on Cardiac Structure and Metabolism. University Park Press. Baltimore. Urban and Schwarzenberg. Munich. 1972 (b).

Remes,K., Kuoppasalmi,K., Adlercreutz,H.
Effect of Long-Term Physical Training on Plasma Testosterone, Androstenedione, Luteinizing Hormone, and Sex-Hormone-Binding Globulin Capacity.
Scan. J. Clin. Lab. Invest. 39. 743-749. 1979.

Ruzicka,L.
Relationships in the Sex Hormone Groups.
Nature 137. 260-262. 1936.

Ruzicka,L. Tschopp,E.
Über die küstliche Herstellung und die physiologischen Wirkungen des männlichen Sexualhormons
Schweiz.Med.Wschr. 64. 1118-1120. 1934.

Seliverstov,S.A.
The Effect of Nerobolon on the Blood Supply, Cardiac Activity, and Haemodynamics.
Farmakol. Toksikol. 32. 59-62. 1969.

Selye,H.
La evolution del concepto del stress.
Folia Clin Int. 32, 471-489. 1969.

Sexualhormone VII.
Über die künstliche Herstellung des Testikelhormons Testosteron (Androsten-3-on-17-0l)
Helv.chim.Acta 18. 1264. 1935.

Sexualhormone X.
Herstellung d. 17-Methyl-testosterons u. anderer Androsten- u. Androstenderivat. Zusammenhänge zwischen chemisher Konstitution u. männlicher Hormonwirkung
Helv.chim.Acta 18. 1487. 1935.

Sexualhormone XXVI.
Zur Kenntnis der Oxydation von Cholesterin-acetat-dibromid mit Chromtrioxyd
Helv.chim.Acta 20. 1291. 1937.

Shillingford,J.P., Joplin,C.F., Jamieson,C.W., Rubens,R.
Visit to Dr. Møller's Clinic.
Bullitin. E.O.C.C.D. 6. 1980.

Short,D.
The Great Circulatory Paradox.
Lancet I. June 11. 1977.

Sobel,H., Marmorston,J.
Hormonal Influences Upon Connective Tissue Changes of Aging.
In: Pincus,G. (ed). Recent Progress in Hormone Research. Vol 14.
Academic. New York. 1958.

Starnes,J.W., Beyer,R.E., Edington,D.W.
Effects of Age and Cardiac Work in Vitro on Mitochondrial Oxidative Phosphorylation and (3H)-leucine Incorporation.
J.Gerontol. 36. 130-135. 1981.

Stryer,L.
Biochemistry.
Freeman, San Francisco, 1975.

Sundhedsstyrelsen (National Board of Health, Denmark)
Dødsårsagerne 1981 (Causes of Death in Denmark 1981).
Vitalstatestik. 1983.

Tweedle,D., Walton,C., Johnston,I.D.A.
The Effect of an Anabolic Steroid on Post-Operative Nitrogen Balance.
Br. J. Clin. Pract. 27/4. 130-132. 1973.

Über d. Synthese d. männlichen Sexualhormons
Verh.Schweizer Naturforsch. Ges. *427*. 1934.

Wagner,H., Zierden,E., Böckel,K., Hauss,W.H.
Correlations Between Lipid and Carbohydrate Metabolism and Testosterone Serum Levels in Patients with Myocardial Infraction.
Acta Endocrinol. (Copenh) (Suppl). 199. 425. 1975.

Weiner,N.
Norepinephrine, Epinephrine, and the Sympathomimetic Amines.
In: Goodman,A.G., Gilman,L.S., Gilman,A. (eds) Goodman and Gilman's The Pharmacological Basis of Therapeutics. 6th edn. McMillan. New York. Chap.8. 1980.

Winther,O.
Testosterone and Fibrinolytic Activity.
Scand. J. Lab. Invest. (Suppl). 99. 207-210. 1965.

Winther,O.
Exercise and Blood-fibrinolysis.
Lancet I. 1195-1196. 1966.

World Health Organization.
Prevention of Ischaemic Heart Disease. Metabolic Aspects.
WHO-symposium, Madrid, 1972, WHO/CVD/73:3.

Yarnell,J.
Visit to Prof. Müller's Clinic, Copenhagen.
Billitin. E.O.C.C.D. 6. 1980.

Zemplényi,T.
Enzyme Biochemistry of the Arterial Wall.
Lloyd-Luke (Medical Books) Ltd. London. 1968.