We wish to thank the following people who co-operated in the study: Dr. M. Podilsky, W. Hrychuk, Research Nurse, and Mrs. F. Taylor, B.A. The study was approved by the Saskatchewan Committee on Schizophrenic Research, and supported by the Department of National Health and Welfare, Ottawa, Canada. Nicospan was supplied by the Wm. S. Merrell Company.

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RÉSUMÉ

La vasodilatation qui accompagne l'administration d'acide nicotinique ne se manifeste que lorsque la concentration de ce produit dans le sang dépasse un certain niveau; elle n'a aucune portée sur l'abaissement de la cholestérolémie. Les auteurs ont employé une nouvelle forme de présentation où la vitamine est conjuguée avec une base spéciale (Nicospan, *marque déposée*) qui permet une libération lente du médicament, prolongée pendant sept à onze heures après l'ingestion. Ils ont pu ainsi dans la majorité des cas supprimer la congestion et la rougeur que plusieurs malades tolèrent mal. Non seulement observa-t-on un abaissement du cholestérol sanguin, mais encore dépassa-t-il celui que l'on obtient par l'administration de doses isolées d'acide nicotinique, rapidement absorbées. Deux malades recevant un gramme trois fois par jour accusèrent des nausées, des vomissements, de la diarrhée et une sensation généralisée de malaise. Ces phénomènes seraient attribuables à l'enrobement de substance plastique des comprimés. Une légère éosinophilie se manifesta chez certains autres.

## Case Reports

# MYOCARDIAL INFARCTION ASSOCIATED WITH HYPERCHOLESTEROLÆMIA IN A YOUNG EUNUCH*

H. Z. POMERANTZ, M.D., F.A.C.P. and N. SHEINER, M.D., *Montreal*

IT IS A WELL accepted fact in medicine that coronary atherosclerosis in persons under 40 is almost exclusively a disease of males.[1-3] Castration increases its incidence and severity in women,[4] while eunuchs are reported to show less atherosclerosis than normal men.[5-7] The high incidence of coronary artery disease in the male and the relative protection of the female have been attributed in large measure to the influence of the gonadal hormones on the distribution of lipids and lipoproteins considered to be etiologically related to atherosclerosis.[8-12]

It is therefore of interest to report the occurrence of myocardial infarction in a young male eunuch with hypercholesterolæmia, and to analyze the significance of such an event with a view to integrating this information with the currently held views outlined above.

A 36-year-old white man was admitted to the Jewish General Hospital because of severe epigastric and retrosternal pain of several hours' duration, associated with sweating and marked restlessness. Nine months earlier he had spent five weeks in another hospital with similar complaints, and a diagnosis of myocardial infarction and duodenal ulcer had been made.

The patient had undescended testicles, and surgical descent of the testicles had been attempted bilaterally at the Michael Reese Hospital in Chicago at the age of 13. The report from there indicated "absent right testicle, small atrophic left testicle brought down into the scrotum."

Ten years previously, at the age of 26, he had started treatment with testosterone both by injection and by subcutaneous implantation of pellets. Treatment was intermittent. He did not start to shave at all until testosterone therapy was started, and at present he shaves only once or twice weekly.

*Family history.*—The only member of his family of whom the patient had knowledge was his father, who was living in Chicago, in good health so far as the patient knew.

*Physical examination.*—His height was 68 inches (172.7 cm.) and his arm span 75 inches (190.5 cm.). There were scanty hair on his face and a female distribution of pubic hair and fat (Figs. 1 and 2). No testes could be found in the scrotal sac.

The blood pressure was 148/105 mm. Hg but soon fell to 100/70 mm. and maintained itself at this level except for a brief dip to 90/60 mm. The lung fields were clear, the heart rhythm was regular, and the sounds were normal. The liver edge was down 1-2 fingers' breadths below the costal margin.

### *Laboratory Data*

The hæmoglobin value on admission was 74% with a hæmatocrit of 37%; one week later the hæmatocrit had become 41% without any specific therapy. White blood cells were 8400 per c.mm.; differential 67% neutrophils, 23% lymphocytes, 5% monocytes and 5% eosinophils. Stools were negative for occult blood. Urine was acid, with a specific gravity of 1.040; it was negative for sugar and showed 1-plus albumin; there were 5-8 red blood cells, 3-6 white blood cells and occasional hyaline and granular casts per high power field.

*From the Department of Medicine, Jewish General Hospital, Montreal, Quebec.

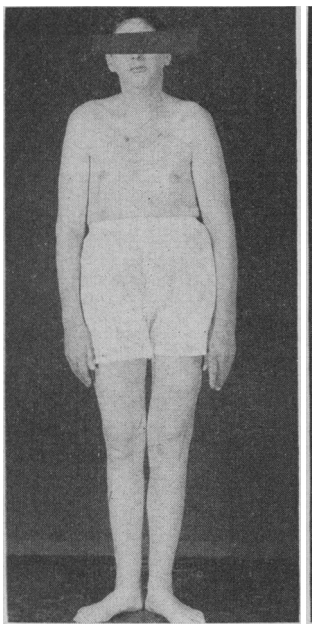

Fig. 1

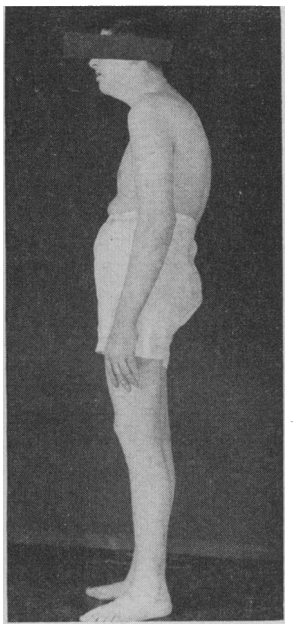

Fig. 2

The non-protein nitrogen level (N.P.N.) was 35 mg. %, post-prandial blood sugar (2-hour) 129 mg. %; serum cholesterol ranged from 270 mg. % to 365 mg. % on repeated determinations. Serum amylase 81 units (normal 80-200), bromsulfalein 16.5% at 45 minutes. Thymol turbidity 5.2 units; thymol and cephalin flocculation 0. Total proteins 6.72 g. % with an albumin of 4.49 g. and a globulin of 2.23 g. The alkaline phosphatase value was 9.5 Bodansky units; bilirubin direct 0.07 unit; total 0.47 unit.

*Electrophoretic pattern of proteins.* – Total proteins 7.41 g. %; $\alpha$-1 globulin 0.29; $\alpha$-2 globulin 0.64; $\beta$ globulin 0.99; $\gamma$ globulin 1.99 g. Serum transaminase was 76 units (normal up to 40); protein-bound iodine 5.9 $\mu$g. % (normal 4-7.5 $\mu$g.); total lipids 1140 mg. %; phospholipids 156 mg. %; urinary corticoids 2.29 mg. for 24 hours (normal 3-9 mg.), 17-ketosteroids less than 0.1 mg. in 24 hours on one determination and 3.6 mg. in 24 hours on a second determination (normal 8-20 mg.). Four-hour ACTH test: the eosinophil count fell from 444 to 143 (normal more than 50% reduction). The corticoids were 1.69 mg. and the 17-ketosteroids undetectable. The creatinine was 0.73 g. per 24 hours (normal 1-1.8 mg.). Follicle stimulating hormone test was positive at 52.8 mouse units per 24 hours (normal 5-50 m.u.). Pregnandiol 1.4 mg. per 24 hours, which is normal for a man. Œstrogen positive at 40 m.u. per 24 hours (normal 40-160 m.u.). Sex determination from examination of leukocytes and buccal mucous membrane was male. Serial electrocardiograms revealed a pattern of posterior myocardial infarction (Figs. 3, 4 and 5).

*Course and therapy.*—The patient was placed on complete bed rest, oxygen administration and sedation. During his stay in hospital he was free of chest pain. Anticoagulants were withheld because of the history of ulcer. During his hospital stay he also developed an acute exacerbation of a chronic otitis media. Otherwise his course was uneventful and he was discharged after six weeks in hospital.

## DISCUSSION

The point of interest here is that this young man, rather than being protected against atherosclerosis, suffered a myocardial infarction despite low levels of male hormone for many years. These low levels are illustrated by the eunuchoid build, the absence of beard until the age of 26, and the low urinary 17-ketosteroid levels found during previous and present hospitalizations. Since castration with diminution of male hormone is apparently protective against coronary atherosclerosis,[4-8] the inference here is that the cholesterol and lipoprotein levels in this patient were so elevated that severe atherosclerosis and myocardial infarction occurred nonetheless. Table I illustrates

TABLE I.

| *$S_f$ group* | *Amount of lipoprotein in mg. %* |
|---|---|
| 0 - 12 | 688 |
| 12 - 20 | 134 |
| 20 - 100 | 236 |
| 100 - 400 | 144 |

the greatly elevated levels of all the Svedberg flotation groups in this case. The œstrogen and pregnandiol levels were normal for a male.

The protective effect of increasing œstrogen or of diminishing male hormone appears to depend on shifts in the lipoprotein distribution, so that the ratio of high-density to low-density lipoprotein is increased.[8-10] The protection of women against atherosclerosis is also explained on this basis.

However, in patients with hypercholesterolæmic xanthomatosis, the ratio of females with atherosclerosis is almost identical with that of males,[13-15] implying that a marked increase in significant lipoproteins militates against the effectiveness of the female hormone in protecting against atherosclerosis. What has been said above suggests that a metabolic balance exists in atherosclerosis. This balance would appear to consist of the gonadal hormones with their effect on lipoprotein distribution, on the one hand, and the constitutional, metabolic and possibly dietary factors which determine the lipoprotein pattern in an individual, on the other hand. If this balance is upset either in the direction of diminished male hormone (viz. castration or eunuchoidism) or increased œstrogen in "normal" men, then the net result appears to be "anti-atherogenic".

However, in the presence of an abnormal lipid pattern based on a constitutional or metabolic defect as illustrated in this case, hormonal variations may be relatively ineffective; instead of a reduction in atherosclerosis, myocardial infarction may actually occur at a young age despite a long-standing decrease in male hormone.

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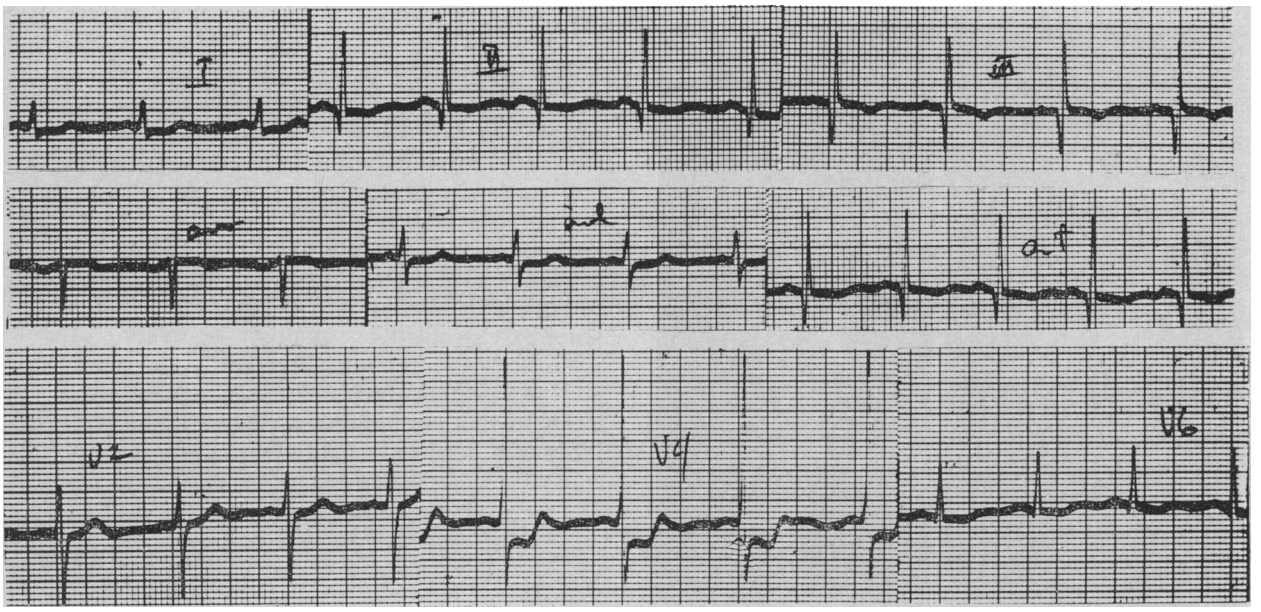


Fig. 3

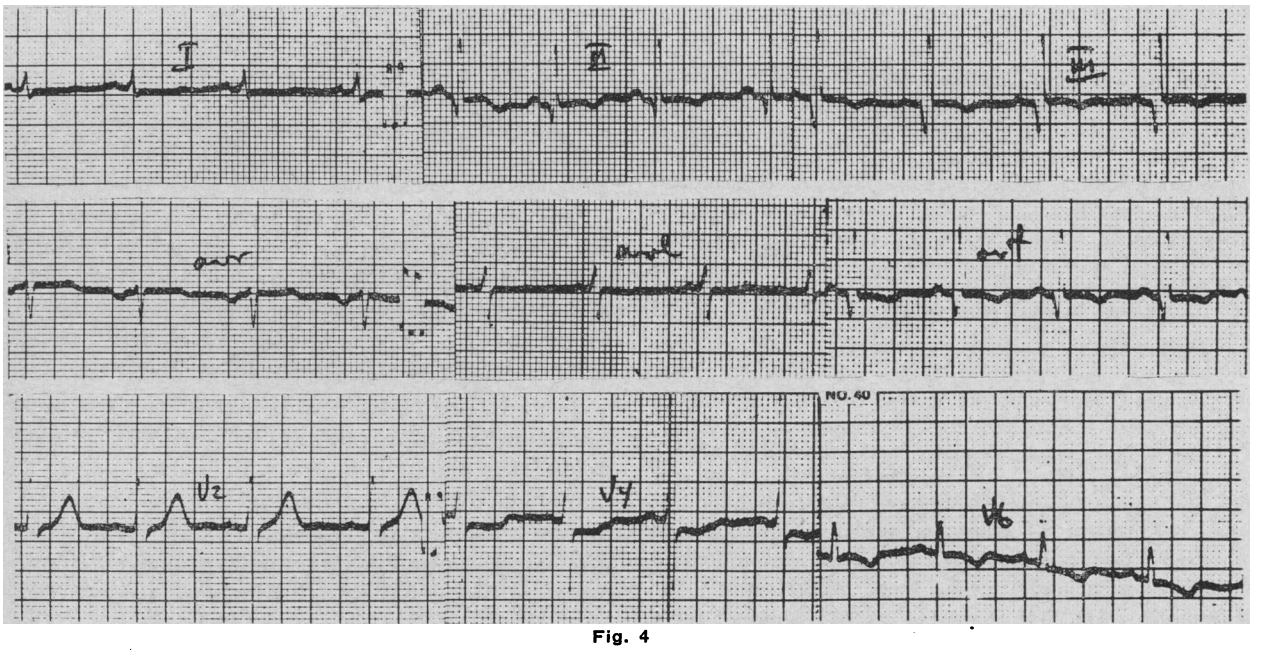


Fig. 4

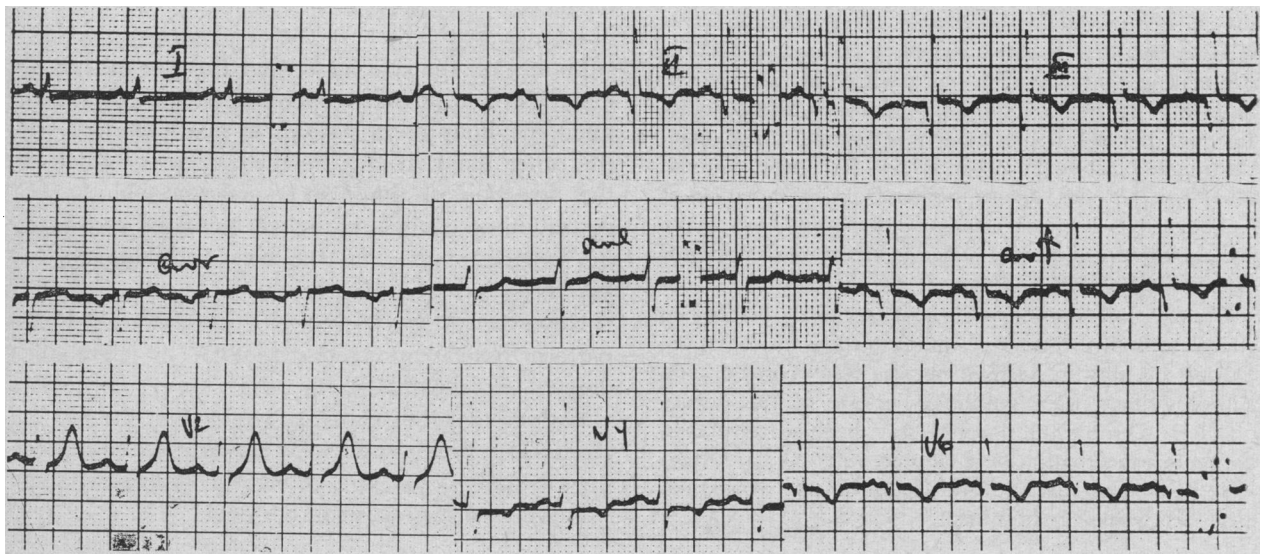


Fig. 5
E.C.G. showing evolution of myocardial infarction.

SUMMARY

A case report is presented illustrating the occurrence of myocardial infarction in a young male eunuch with essential hypercholesterolæmia.

The effect of the gonadal hormones on lipoprotein distribution is discussed, and the absence of the expected protection against atherosclerosis conferred by the eunuchoid state is attributed to the associated defect (essential hypercholesterolæmia) which apparently is pre-eminent in rendering ineffectual the expected beneficial effects of a hypogonadal state on lipoprotein distribution and the degree of atherosclerosis.

We wish to acknowledge the technical help received from the Department of Biochemistry of the Jewish General Hospital under the direction of Dr. R. Schuchar, as well as to thank Dr. R. F. Robertson and the staff of the ultracentrifuge laboratory of the Department of Chemistry, McGill University, for their determinations of the Svedberg flotation numbers of the lipoproteins.

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## SCLEREMA NEONATORUM: REPORT OF AN UNUSUAL CASE*

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THERE ARE TWO conditions in infancy to which the term "sclerema neonatorum" has been applied. Readers are referred to the work of Wickes[13] for a detailed description of both.

One is an acute diffuse hardening of the skin (referred to as acute generalized sclerema in this paper) of unknown etiology occurring usually in the newborn period but also at times later in infancy after acute dehydration. This syndrome is associated with a poor clinical condition (cyanosis, respiratory difficulties, etc.) and in the absence of treatment has a very bad prognosis. Pathologically, either nothing abnormal is found or there is merely a slight increase in the subcutaneous connective tissue bands. Cases of this nature have been well reviewed by Hughes and Hammond.[11]

The second condition is a benign circumscribed hardening of the skin (referred to as benign circumscribed sclerema in this paper) in which trauma is a causative factor. This syndrome may properly be described as neonatorum since it appears within the first week of life. The lesion undergoes resolution over a period of a few months, at times by cyst-like formation and occasionally by calcification. Pathologically, the subcutaneous fat shows gross degeneration and reacts chemically as neutral fat. There is giant cell formation and lymphocytic infiltration in the connective tissue septa. This specific pathological lesion is called subcutaneous fat necrosis, and this term is becoming more and more restricted in its use to describe the pathological lesion rather than the clinical condition.

In an intermediate position between these two clearcut entities are mixed forms of sclerema. These rare cases are characterized by the combination to some extent of the clinical and pathological features of both simultaneously or in succession.

It is the purpose of this paper to report one of these mixed forms recently seen here, and to cite a similar case from the literature.

### REVIEW OF LITERATURE

For an excellent and comprehensive review of the literature on the subject, especially concerning the evolution in conception of these syndromes and the confusion through which the terminology has gone, the reader is referred to the work of McIntosh, Waugh and Ross.[10] The history of the condition may be summarized as follows.

Usenbenzius[1] probably first described the syndrome of acute sclerema in 1718, and Underwood[2] in 1784 included this entity for the first time in a "Treatise on the Diseases of Children"; in a second edition in 1819, he called it "skin bound". The term "sclerema" was first introduced into the literature in 1812 by Chaussier[3] in France. The histological picture of "subcutaneous fat necrosis" was well described by Fabyan[4] in 1907, and applied to designate "benign sclerema" by Bernheim-Karrer[5] in 1922. The theory that trauma is a pathogenic factor in this condition was put forward by Cruse[6] in 1879, and substantiated by the experiments of Farr[7] on pigs in 1923, and of Lemez[8] on infants in 1928.

The biochemical nature of the subcutaneous fat in this latter syndrome was studied extensively by Channon and Harrison[9] in 1926. Further important steps in the study of these syndromes were made by Hughes and Hammond[11] in 1948; they gave, with a review of the cases in the literature, a clear exposition of the pathology of "acute generalized sclerema". In 1948 also, Flory[12] collected two cases of generalized fat necrosis (subcutaneous and visceral) from the literature and described one of his own. He suggested the interesting possibility that the few cases of so-called "benign sclerema" with fatal outcome may have been cases of patho-

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