conservative treatment, and can be radically accelerated with the restoration of a near normal blood flow only by direct arterial surgery. The direct operative approach may be worth considering in aorto-iliac lesions where the long-term results are good, but in general the long-term outcome of arterial surgery below the inguinal ligament is not yet satisfactory enough to warrant this form of treatment when claudication is the only symptom.

Sympathectomy exerts its maximal influence on the blood supply to the skin, and if the arterial inflow into the area is not overwhelmingly reduced, then sympathetic denervation should be followed by a worth-while increase in cutaneous blood flow. This concept is supported by the results in this clinical study, and our patients with early nutritional disturbance benefited from sympathectomy. We regard mild rest pain and associated sensory disturbances, with or without areas of localized gangrene, as indications for the operation. Sympathectomy is, however, ineffective in the more advanced stages of developing major gangrene, and it is in this latter group of patients, in whom loss of the limb is threatened, that we believe direct arterial surgery has an important place.

Summary

412 patients with atherosclerosis of the arteries of the lower limb were followed for periods varying from 3 to 12 years. The mortality rate during the period of observation was 21% and the overall limb-amputation rate was 10%. Certain factors influencing the fate of the limb are described. The outcome in patients treated by lumbar sympathectomy is compared with that of similar patients not treated surgically. Sympathectomy did not materially alter the long-term result when performed for intermittent claudication but was beneficial at the stage of early nutritional impairment.

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The Hospitals Year Book, 1962, has been published by the Institute of Hospital Administrators. The hospital directory sections give full particulars of hospitals and hospital authorities in Great Britain, Northern Ireland, and the Isle of Man. Other sections provide details of bed and patient statistics, hospital finance, Government departments, and statutory bodies, organizations concerned with hospital and health services, local health authorities, executive councils, the N.H.S. Whitley Councils, and hospital contributory and provident schemes. The substantial reference section includes notes for hospital administrators on legal, technical, and general subjects, as well as detailed indexes to statutory instruments and official circulars, summaries of reports, and a short bibliography of hospital literature. As in previous years the final section consists of a comprehensive guide to hospital purchasing. In his review of "Some Current Developments and Problems" the editor, Mr. J. F. Milne, discusses the hospital building programme. He also comments on the effects of the Mental Health Act, and discusses aspects of the geriatric services, efficiency studies, and the welfare of patients. (Price 63s., postage 2s. 9d. from the I.H.A., 75 Portland Place, London W.1.)

PREVALENCE OF CORONARY ATHEROSCLEROSIS IN NORTHERN INDIA

BY

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The aetiology of coronary heart disease continues to remain obscure. Intensive clinical and experimental research from all over the world during the last four decades (since the first world war) has yielded only inconclusive and sometimes conflicting results. More recently, greater attention has been paid to the social and epidemiological studies in this field. In its first report, the World Health Organization's Expert Committee on Cardiovascular Diseases and Hypertension (W.H.O., 1959) emphasized the need to find the incidence of coronary artery disease in all countries. It has been reported that atheroma and coronary heart disease are very uncommon in Asiatics as compared with Europeans (Arnott, 1954; *Lancet*, 1955). So far as clinical evidence is concerned, it was reported by one of us (Malhotra and Pathania, 1958) that not only is coronary heart disease not uncommon in this part of India but its general pattern also broadly conforms to the descriptions given by Western authors. The present investigation was conducted in order to determine the prevalence of coronary atherosclerosis in the general population in this extreme northern part of India. An attempt was also made to find whether there was any correlation between its severity and such factors as age, sex, urban and rural distribution of cases, and dietary habits.

Material and Method

Coronary arteries were studied histopathologically in 151 necropsies during the period 1955-8. The age-groups of the subjects ranged from infancy to the seventh decade. The hearts were removed at medico-legal post-mortem examinations of apparently healthy persons who had died as a result of accidents, murders, suicides, or poisoning. It was thought that a study of this type would more truly reflect the prevalence of coronary atherosclerosis in the general population than investigations on hospital necropsy material. Any case in which associated disease, such as tuberculosis or malignancy, was discovered at necropsy was excluded, as such diseases are known to affect the development of atheroma (Lober, 1953).

Since any relevant information beyond age, sex, and residence (urban or rural) was not available from the necropsy protocols, socio-economic details and dietary

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habits, etc., of the deceased were obtained from the close relatives and friends who accompanied the body.

The hearts were fixed and preserved in 10% formalin. The three major coronary arteries were dissected out and the length of each artery was measured. Each artery was then sectioned by multiple closely spaced cuts with a scalpel and the lumen opened with scissors. The exposed arterial wall was carefully examined for any thickening, yellow streaks, frank plaque, or calcification. Such pieces as showed the maximum degree of gross change were taken for histological examination. A minimum of eight pieces were obtained in each case—three from each of the two principal arteries and two from the circumflex branch. In case gross changes were absent, the three pieces were taken one each from the proximal 1 in. (2.5 cm.), the middle portion, and the terminal 1 in. (2.5 cm.) of each artery (from the proximal and middle portions in the case of circumflex).

The sections were routinely stained with haematoxylin, eosin, and orcein elastic tissue stain and, if necessary, also for fat (sudan IV) and connective tissue (Mallory's stain). All the histological sections were seen by one of us (N. L. C.) and graded for atheroma (grades I-IV) according to the criteria laid down by the Expert Committee on Cardiovascular Diseases (W.H.O., 1958).

In grade I were placed only such sections as showed very early or minimal changes which cannot with certainty be taken as evidence of atheroma (Wilens, 1951). At the other extreme, grade IV changes implied marked narrowing or occlusion of the lumen with calcification, haemorrhage, or thrombus formation. Grade II changes were interpreted as moderate and grades III and IV as severe, and both these represented significant atheroma. The grade allotted to a particular artery was the one which corresponded with the most advanced change among the various pieces obtained from that artery. Likewise, an individual case was given the highest grade representing the most advanced atheromatous change observed in any one of the three major vessels.

Results

Prevalence of Atherosclerosis in Relation to Age and Sex.—Of the 151 hearts studied, 123 were from males and 28 from females. All the cases were divided into age groups according to the age at death. The degree of atheroma encountered in different age-groups and in the two sexes is shown in Table I. Significant atheroma was present in nearly two-thirds (64%) of those above the age of 20, and, except for the fifth decade, there was a gradual increase in both its frequency and severity from the second to the sixth decade. Maximum incidence was in the sixth decade (89.5%) and there was a decline to 77.8% in the seventh decade. Among males, significant atheroma was present in 49 (71%) of

the 69 above the age of 30, the change being severe in 23 (33%).

Distribution of Atheromatous Lesions.—Of the 79 cases with significant atheroma, both the principal coronary arteries were involved in 60 (76%), and in 50 (63%) of these 60 the sclerosis was of equal severity in the two arteries. Atheroma was confined to the left coronary in 18 cases and right coronary in one case.

Sex Difference in Atherosclerosis.—The small number of female cases available in the whole series generally, and in each individual decade particularly, precludes the drawing of any valid comparison with regard to the degree of atherosclerosis in the two sexes. However, it was observed that all except one of the eight female subjects above the age of 30 had moderate or severe coronary atherosclerosis. The various histological sections in these cases were carefully studied, and it was our impression that, unlike what is seen in clinical coronary heart disease, no appreciable difference existed in the two sex groups in either the frequency or the severity of atheroma. In most of the other necropsy studies a similar finding is reported, which lends itself to the hypothesis that besides atherosclerosis there is probably some factor (? hormonal, ? genetic) that may be responsible for the greater prevalence of clinical coronary heart disease in the males.

Correlations Between Atherosclerosis and Certain Socio-economic and Other Factors

These correlations are all based on the information supplied by friends or relations of the deceased and are therefore only indirect.

Religion.—Hindus and Sikhs are the two main communities in this part of the country, with the latter preponderating in the rural areas of this and the adjoining districts. The incidence of coronary athero-

TABLE II.—Atherosclerosis and Different Religions

Religion	Total No. of Cases	Positive Cases	
		No.	%
Hindus	45	24	53.2
Sikhs	101	52	51.5
Others (Christians and Moslems) ..	5	3	60.0

sclerosis was found to be almost exactly similar ($P=65\%$ approximately) among them (Table II); this was not surprising, since ethnically both these communities and also the remaining five cases have the same origin and no significant difference exists between the Hindus and Sikhs in respect of diet and other social and environmental conditions. In his observations on persons of Indian origin in Singapore, Muir (1960) reported that the Sikhs are liable to die from coronary heart disease one and a half times and the Moslems twice as often as their non-Moslem compatriots, who

TABLE I.—Degree of Atheroma Correlated with Age and Sex

Age-group	None			Grade I			Grade II			Grade III			Grade IV			Total			Significant Atheroma (Grades II-IV)	
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	No.	%
0-10	10	6	16	0	1	1	0	1	1	0	0	0	0	0	0	10	8	18	1	5.5
11-20	9	2	11	2	1	3	1	1	2	2	0	2	0	0	0	14	4	18	4	22.2
21-30	9	5	14	6	0	6	6	1	7	2	9	2	0	0	2	30	8	38	18	47.4
31-40	1	0	1	6	0	6	10	1	11	4	1	5	1	0	1	22	2	24	17	70.8
41-50	2	0	2	8	0	8	10	1	11	3	1	4	0	0	0	23	2	25	15	60.0
51-60	0	0	0	1	1	2	4	0	4	6	1	7	5	1	6	16	3	19	17	89.5
61-70	1	0	1	1	0	1	2	0	2	3	1	4	1	0	1	8	1	9	7	77.8
Total	32	13	45	24	3	27	33	5	38	25	6	31	9	1	10	123	28	151	79	52.4

included Hindus, Christians, Buddhists, and others. It is, however, not stated whether the Hindus included in this series were chiefly from the Northern or Southern parts of India, and the dietetic habits of people and probably the incidence of coronary disease also vary widely in different parts of India. The Sikhs, on the other hand, were certainly from Northern India.

Urban versus Rural.—The majority of the cases belonged to the rural areas (Table III). It was interesting to find that among the cases who had significant atheroma no appreciable difference ($P=35\%$ approximately) existed in the percentage of cases living in urban

TABLE III.—Distribution of Cases in Urban and Rural Areas

	Total No. of Cases	Positive Cases	
		No.	%
Urban	31	15	48
Rural	105	55	52
Unknown	15	9	60
Total	151	79	52.4

and rural areas. Whether clinical coronary heart disease and coronary atherosclerosis run parallel or not remains to be worked out. We are presenting only the data so far as atherosclerosis is concerned. The correlation with prevalence of clinical coronary heart disease cannot at present be attempted, as an extensive survey in the rural areas in regard to this aspect of the problem is not yet within our financial resources.

Diet.—In 36 cases either the details of the diet were not known or the age of the subject was under one year. The dietetic habits of 115 cases is shown in Table IV. The diet of an average Punjabi is about 2,000–2,500 calories, of which fats contribute approximately 20%. Chapatties made from wheat “atta” along with pulses

TABLE IV.—Atherosclerosis and Diet

	No. of Cases	Positive Cases	
		No.	%
Vegetarian	35	15	43
Non-vegetarian	80	41	51

and cooked vegetables constitute the main items. The non-vegetarians eat mutton, but usually not more than once a week or so. On the other hand, milk and curd are consumed in plenty, especially by people in rural areas. Practically all the cooking is done in “ghee” (clarified butter). Though much to be desired, satisfactory and reliable details of the diet of the deceased were difficult to obtain, especially in regard to the total calories consumed and the quality and proportion of fats in it. Therefore no attempt has been made to define the diet beyond its vegetarian or non-vegetarian character. In the non-vegetarian group were included all those who took meat occasionally or frequently: 61 consumed meat only once a fortnight or so, in 17 the details were not known, while only two ate meat daily. Most of the non-vegetarians were therefore virtually non-meat-eaters, and this makes it difficult to draw any definite conclusion regarding the incidence of atherosclerosis between vegetarians and non-vegetarians. The study does, however, show that vegetarianism by itself is not much of a protection so far as the development of coronary atherosclerosis is concerned.

Discussion

In recent years many epidemiological surveys have revealed wide interracial differences in the prevalence

of ischaemic heart disease. Necropsy studies of coronary atherosclerosis are not available from as many different countries, but here, too, wide variations in incidence are known. While severe atherosclerosis of coronary arteries is rare in Okinawans (Steiner, 1946), the Japanese living in Japan (Keys *et al.*, 1958), and the South African Bantu (Higginson and Pepler, 1954), it is common among the whites in South Africa (Hannah, 1958) and in Japanese living in Los Angeles. These differences in prevalence have been stated to be in relation to the amount of calories provided by fats in the diet and explained on the basis of lower levels of serum cholesterol in peoples with a lower incidence of coronary disease (Keys *et al.*, 1958).

From Western countries several necropsy series have been recorded, but in few of them was death attributable to accidental causes. Among 300 young apparently healthy American soldiers killed in the Korean war, Enos *et al.* (1953) found some evidence of coronary atherosclerosis in 77.3%. In 35% of them, however, the changes were insignificant. White *et al.* (1950), in routine hospital necropsies on male subjects, reported a severe degree of coronary atherosclerosis (grade III or more, on a basis of Grade I–IV of the present series) in 70–80% of people in the sixth decade. It is significant that the corresponding figure (68.7%) in the present series is only slightly lower. Significant atheroma was present in 72% of the males above the age of 30, the sclerosis being severe (grade III or more) in one-third of the cases. And since in 63% of the cases the changes in the left and right coronary arteries were of equal degree, the implication is that nearly one out of every three apparently healthy males above the age of 30 has a rather severe degree of coronary sclerosis, usually generalized, at least in this part of India. We therefore find it difficult to agree with the views held by some Western writers (Arnott, 1954) that atheroma and coronary heart disease are “comparatively very uncommon” in India and other Oriental countries.

The maximum incidence and severity of atheroma were observed in the sixth decade. This finding would seem to run parallel with the clinical observations from this institution (Malhotra and Pathania, 1958) that the highest incidence of coronary heart disease is also in the sixth decade.

As already stated, no great difference in the prevalence of significant atherosclerosis was found in the two sexes or in the urban and rural population groups.

Summary

A histopathological study of coronary arteries in 151 cases of accidental death is presented and the degree of atherosclerosis observed is correlated with age. The incidence of atherosclerosis rose steadily with age up to the sixth decade. Significant coronary sclerosis was found in approximately two-thirds of the subjects above the age of 20 years, and nearly one out of every three apparently healthy males beyond 30 had a rather severe grade of coronary sclerosis. These findings are consistent with the conclusion that significant atheroma of the coronary vessels is quite common in this part of India, both in the young and in the aged.

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SEQUENTIAL TRIAL OF ISOCARBOXAZID IN ANGINA PECTORIS

BY

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The evaluation of a new type of compound in the treatment of angina pectoris is well recognized as being difficult. Since the introduction of monoamine oxidase (M.A.O.) inhibitors the first successes claimed have not been confirmed and subsequent reports have been conflicting. The problems involved have been surveyed in a leading article in the *British Medical Journal* (1960). The initial reports on many of these compounds have not been concerned with a control series, and later studies with a double-blind technique have been less enthusiastic. Some effect upon the symptom of angina seems probable, however, and a search is being made for further compounds of this series with fewer side-effects and greater efficacy. Controlled trials are still necessary, therefore, to reach a conclusion on the value and place of these drugs in the routine treatment of angina.

The results of a controlled assessment of isocarboxazid ("marplan"; 3-benzylhydrazinocarbonyl-5-methylisoxazole) is reported below, and a brief attempt is made to assess clinical factors that might have influenced response.

Material and Method

Selected out-patients with a convincing history of angina pectoris were considered for the trial as they became available. The statistical method, an open sequential procedure as described by Armitage (1960), determined its design and the assessment of results.

For admission it was necessary for the patient's angina to be regarded clinically as due to coronary artery disease and to be of at least moderate severity with relief by trinitrin. Severity was recorded on the criteria of Wood (1956), and the following grades were accepted: II, pain on walking on level at average speed; III, pain on walking slowly, and IV, pain at rest.

In addition, the patient's angina had to be static for at least three months, and so far as was possible neurotic and unreliable witnesses were excluded at the outset. A history of cardiac infarction less than six months

previously was not acceptable. Cardiographic abnormalities were regarded as necessary for the diagnosis only in clinically doubtful cases. Before and after treatment each patient had blood-pressure estimations and an electrocardiogram. Patients taking nitrites had their drugs continued but barbiturates and tranquillizers were omitted.

A series of 63 patients began the trial, but eight of them failed to finish for varied reasons—development of cardiac infarction, non-cooperation, and death. The remaining 55 were considered for analysis. The trial was conducted on the double-blind basis, using control tablets identical in appearance to isocarboxazid, and the crossover-within-patient technique was employed, each patient acting as his own control. The treatment given was one tablet three times daily before meals, and was unknown to both patient and observer. The total daily dosage of isocarboxazid was 30 mg. For administrative purposes patients were placed in groups of five, the key for which was opened and the group assessed after completion of both treatments. Each treatment was given for four weeks with a three-weeks interval between, so as to eliminate any possible prolongation of affect from one to the other. The initial treatment was allocated randomly. After each treatment the patients were interviewed and asked to state if they felt any change in their angina, and, if so, was this definite or slight. Minor degrees of help claimed were counted as failures, and only definite statements of marked improvement were accepted as a success.

The statistical plan had to satisfy the power $1 - \beta = 0.95$ of detecting a difference between the two treatments with a two-sided significance level $2\alpha = 0.05$ when the following success rates were adopted. It was expected there would be a favourable response to the control in 40% of patients, $p_1 = 0.4$, and it was thought that if 68% responded favourably to isocarboxazid, $p_2 = 0.68$, the trial could be accepted as a success for this treatment. With these two proportions Fig. 2 of Armitage (1954) gives a value for $\theta = 0.75$; that is, the proportion of united pairs which must be obtained in the trial to indicate success for isocarboxazid. For this critical value of θ the limits of the boundaries in an open sequential design were obtained from Table 3.1 of Armitage (1960).

Results

Table I gives details of the response of the groups to treatment, the untied pairs of which are plotted on the sequential design. A significant preference for isocarboxazid was obtained in spite of a large proportion of failures with both treatments.

As expected the milder cases of angina showed more reaction to the placebo, and tied pairs in whom both treatments were successful were all in this group. In grades III and IV 40% of patients showed a preference for isocarboxazid, whereas in grade II only 27% did so. Males responded more favourably than females—37% to 23%. Neither the patient's age nor the duration of angina had any effect on the outcome, the averages of all groups lying inside the standard deviation of the series. The height of systolic blood-pressure was likewise unimportant, there being little difference between the proportion of patients responding in the upper or lower ranges, percentages being 39 and 36.4 respectively. Analysis of the cardiographic patterns showed that patients with major ischaemia but without definite infarction obtained benefit in 58% of cases. This is a