# THE PROBLEM OF CORONARY HEART DISEASE WITH SPECIAL REFERENCE TO THE INFLUENCE OF PHYSICAL ACTIVITY* 

C. H. Wyndham, D.Sc. (Rand), M.B., M.R.C.P. (Lond.), F.R.S.S.AF., Human Sciences Laboratory, Chamber of Mines of South Africa, Johannesburg

Coronary heart disease has reached epidemic proportions in many western nations. One estimate is that 'premature cardiac deaths during the productive years below 65 occur at the staggering rate of 250,000 per annum in the USA:.

A number of prospective epidemiological studies were started in the 1950s in the UK and USA with the object of obtaining reliable figures on the incidence of coronary heart disease in relation to age and sex, and of trying to identify the main causal factors. Some idea of the influence of age and sex on the incidence of coronary heart disease in the USA is contained in Table I, quoted from a paper by Kannel et al. on the Framingham study. ${ }^{\text {a }}$ The incidence for males, over the whole age span, was 761/100,000/year.

TABLE 1. EIGHT-YEAR INCIDENCE OF CORONARY HEART DISEASE

| Age and sex <br> at risk | New cases <br> CHD | Incidence rate <br> (per 1,000) |  |
| :---: | :---: | :---: | ---: |
| Men | 825 | 20 | $24 \cdot 2(3 \cdot 0$ p.a.) |
| $30-39$ yrs | 8750 | 51 | $66 \cdot 2(8 \cdot 3$ p.a.) |
| $40-49$ yrs | 770 | 81 | $131 \cdot 2(16 \cdot 4$ p.a.) |
| $50-59$ yrs | 617 | 1 | $1 \cdot 0(0 \cdot 1$ p.a.) |
| Women | 1,036 | 19 | $19 \cdot 9(2 \cdot 5$ p.a.) |
| $30-39$ yrs | 955 | 53 | $66 \cdot 9(8 \cdot 4$ p.a.) |
| $40-49 \mathrm{yrs}$ | $90-59$ yrs | 792 |  |

What is not generally realized is that 1 in 5 cases of coronary thrombosis ( $19.6 \%$ ) is immediately fatal. Another $16 \%$ die within the first few days after admission to hospital in spite of every therapeutic aid. The over-all 'immediate' fatality rate is an appalling $35 \%$, or 1 in 3 cases of coronary heart disease, according to Kannel et al. ${ }^{2}$ Because of the high proportion of deaths within a few days of the occurrence of coronary thrombosis, there is little likelihood of the salvage of many cases by improvements in therapeutics. As Kannel et al. ${ }^{2}$ put it so well: 'Hope appears to lie in the prevention of the disease in the more susceptible individual' (provided the causal factors can be identified).

In addition to the loss of manpower by death during an individual's most productive period, even the cases which recover from an attack of coronary thrombosis are often below their former level of productivity because of inadequate or improper rehabilitation. The cost to western countries of the mortality and morbidity of coronary heart disease is enormous. The cost of training a jet pilot is said to be R100,000. It would be interesting to estimate the cost to the State and commerce of the death in his 40 s of a well-trained and experienced executive. Raab, ${ }^{1}$ in a recent paper, estimates that coronary heart disease costs the USA about 4.2 billion dollars annually.

A recent survey of the Health Advisory Board of the Public Health Department in the Republic of South Africa estimates that the mortality rate from coronary heart disease in White males below 45 years is the highest in the world.
*Date received: 18 April 1969.

In this paper the relative importance of some of the major factors which are today known to be implicated in the development of coronary heart disease is examined. A scheme for the early recognition of susceptible individuals is proposed, and suggestions are offered for the preventive measures which shou'd be taken by the individual, and be provided by the State, industry and commerce, if they wish to make an impact on this epidemic which is decimating the most important section of the commurnty from the point of view of the economic life of the Republic.

FACTORS ASSOCIATED WITH A HIGH INCIDENCE OF CORONARY HEART DISEASE
Recent prospective epidemiological studies have identified a number of factors as being associated with a high incidence of coronary heart disease, viz.: (i) physical inactivity, (ii) high serum cholesterol levels, (iii) hypertension, (iv) heavy smoking, and (v) obesity.

## Physical Inactivity

Morris et al., in their report in $1953,{ }^{3}$ on the incidence of coronary heart disease in London bus conductors and drivers, were the first to show unequivocally that 'men in physically active jobs (bus conductors) have a lower incidence of coronary heart disease than men in physically inactive jobs (bus drivers) . . more important, the disease is not so severe in the physically active workers, tending to have a smaller case fatality and a lower early mortality rate'. Their findings have since been confirmed in a number of large-scale prospective epidemiological studies in the USA, such as Breslow and Bueli's study in California, ${ }^{4}$ Taylor and co-workers' examination of the incidence of coronary heart disease in 2 groups of railway workers, ${ }^{5}$ Kahn's study of postmen and clerks in the postal services in Washington, ${ }^{6}$ and the study by Frank et al. of 11,000 persons in the Health Insurance Plan of Greater New York, reported in 1966. ${ }^{\text {. }}$ They found a striking association between physical inactivity and early mortality for the initial infarction in men of less than 65 years of age. They state further: 'Inquiry about the customary physical activities on and off the job had permitted the delineation of a group of "least active" men who are more likely to experience a clinically severe episode and die within four weeks of its onset than the men who are relatively more active . . . early mortality of the "least active" men was three times that in the group of most active men . . . physical activities off the job have been found to play an important role in this relationship' (my italics).

## Serum Cholesterol Levels

Serum cholesterol is thought to increase from about $180 \mathrm{mg} . / 100 \mathrm{ml}$. in the 20 s to about $220 \mathrm{mg} . / 100 \mathrm{ml}$. in the 50 s. Great emphasis was given to the association between coronary atherosclerosis as a major cause of coronary heart disease and an association between a raised level of serum cholesterol, and an increased incidence of
coronary heart disease has been well documented in a number of studies in the USA. This is shown in Table II, taken from a review by Keys and Blackburn on this subject in 1963.'

TABLE 11. SERUM CHOLESTEROL LEVELS AND SUBSEQUENT DISEASE

|  | $\begin{array}{l}\text { Age at } \\ \text { start }\end{array}$ | $\begin{array}{c}\text { Years }\end{array}$ | $\begin{array}{c}\text { Serum } \\ \text { chol. }\end{array}$ | $\begin{array}{c}\text { \% of Rate of } \\ \text { men }\end{array}$ |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Area and ref. | $\begin{array}{c}\text { (yrs) }\end{array}$ |  |  |  |  |
| followed |  |  |  |  |  |$)$

The close association between a high intake of saturated fats in the diet and the incidence of coronary heart disease is obvious in Table III, taken from Jolliffe's review in 1969. ${ }^{\text {. }}$

TABLE III. ASSOEIATIOV BETWEEN INTAKE OF SATURATED FATS AND INCIDENCE OF CORONARY HEART DISEASE

|  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| USA | $704 \cdot 7$ | 3,070 | 39.2 | $33 \cdot 5$ | $8 \cdot 2$ |
| Australia | $577 \cdot 4$ | 3,160 | $37 \cdot 9$ | $34 \cdot 7$ | $7 \cdot 3$ |
| Austria | 283.9 | 2,820 | $31 \cdot 3$ | $23 \cdot 9$ | $5 \cdot 8$ |
| Belgium | $250 \cdot 1$ | 2,980 | $35 \cdot 0$ | $24 \cdot 4$ | $5 \cdot 7$ |
| Canada | $588 \cdot 3$ | 3,130 | $38 \cdot 0$ | $35 \cdot 0$ | $8 \cdot 0$ |
| Ceylon | $103 \cdot 4$ | 1,980 | $15 \cdot 2$ | 11.8 | $2 \cdot 2$ |
| Chile | $267 \cdot 3$ | 2,490 | $19 \cdot 8$ | $12 \cdot 0$ | $4 \cdot 3$ |
| Denmark | $294 \cdot 8$ | 3,370 | $38 \cdot 3$ | $25 \cdot 5$ | $6 \cdot 1$ |
| Finland | $621 \cdot 7$ | 3,170 | $31 \cdot 1$ | $28 \cdot 4$ | 6.8 |
| France | $109 \cdot 9$ | 2,850 | $29 \cdot 5$ | $20 \cdot 7$ | $6 \cdot 4$ |
| German Fed. | $313 \cdot 7$ | 2,950 | $35 \cdot 6$ | $23 \cdot 0$ | $5 \cdot 6$ |
| Italy | $226 \cdot 8$ | 2,550 | $22 \cdot 3$ | $10 \cdot 5$ | $3 \cdot 6$ |
| Japan | $122 \cdot 5$ | 2,005 | $7 \cdot 9$ | 1.4 | $2 \cdot 6$ |
| New Zealand | $525 \cdot 7$ | 3,370 | $39 \cdot 8$ | $37 \cdot 6$ | $8 \cdot 2$ |
| Norway | 248.8 | 3,130 | $38 \cdot 0$ | $17 \cdot 0$ | $6 \cdot 4$ |
| Portugal | $107 \cdot 7$ | 2,560 | $24 \cdot 5$ | $9 \cdot 4$ | 3.9 |
| Sweden | $294 \cdot 6$ | 3,070 | $39 \cdot 4$ | $28 \cdot 3$ | $7 \cdot 3$ |
| Switzerland | $273 \cdot 0$ | 3,100 | $33 \cdot 6$ | $23 \cdot 6$ | $6 \cdot 6$ |
| United Kingdom | $427 \cdot 5$ | 3,270 | $38 \cdot 4$ | $35 \cdot 0$ | $5 \cdot 9$ |
| Yugoslavia | $68 \cdot 2$ | 2,525 | $19 \cdot 1$ | $13 \cdot 2$ | $2 \cdot 8$ |

There is little doubt that the dietary habits of the majority of South African Whites are similar to those of the countries with a high incidence of coronary heart disease listed in Table III.

The very strong association between serum cholesterol level and incidence of coronary heart disease is well shown in the Framingham study. ${ }^{2}$ The relationship obtained is given in Table IV.

TABLE IV. SIX-YEAR INCIDENCE OF CHD ACCORDING TO INITIAL SERUM CHOLESTEROL LEVEL

| Men 40-59 years | New CHD | Population | Observed rate $/ 1,000$ |
| :---: | :---: | :---: | :---: |
| Less than $210 \mathrm{mg} . / 100 \mathrm{ml}$. | 16 | 454 | 35.2 (5.9 p.a.) |
| $210-244 \mathrm{mg}$. 100 ml . | 29 | 455 | 63.7 (10.9 p.a.) |
| 245 mg .100 ml . or more | 31 | 424 | $120 \cdot 3$ (20•1p.a.) |

From this association it will be clear that when an individual's serum cholesterol rises above $210 \mathrm{mg} . / 100 \mathrm{ml}$. after the age of 40 years, it is a warning signal; when it goes above $250 \mathrm{mg} . / 100 \mathrm{ml}$. there is a clear case for immediate preventive treatment by giving careful attention to diet.

## Hypertension

Both the USA and UK studies have shown that, as with blood cholesterol levels, an increase in the risks of developing coronary heart disease follows a rise in the level of blood pressure. Some workers have expressed the risks in relation to systolic blood pressure, as was done in the Framingham study ${ }^{2}$ (Table V). Others prefer to relate the risks to diastolic blood pressure, as was done in the Los Angeles study (Table VI). ${ }^{20}$

TABLE V. RISK OF DEVELOPING CORONARY HEART DISEASE IN 8 YEARS ACCORDING TO INITIAL SYSTOLIC BLOOD PRESSURE LEVEL

| Subjects | Blood pressure level | Population <br> at <br> risk | $\begin{gathered} \text { New } \\ \text { CHD } \end{gathered}$ | Observed rate/ 1,000 |
| :---: | :---: | :---: | :---: | :---: |
| Men aged 30-59 yrs | 120 | 369 | 8 | 21.7 (2.7p.a. |
|  | 120-139 | 988 | 58 | 58.8 (7.4 p.a.) |
|  | 140-159 | 576 | 41 | $71 \cdot 2$ (8.9 p.a.) |
|  | 160-179 | 194 | 26 | $134 \cdot 0$ (16.9 p.a.) |
|  | $180+$ | 85 | 19 | $223 \cdot 4$ (27.9 p.a.) |
| Women aged $40-59 \mathrm{yrs}$ | 120 | 260 | 2 | 7.6 (0.95 p.a.) |
|  | 120-139 | 629 | 12 | 19.4 (2.4 p.a.) |
|  | 140-159 | 444 | 17 | 37.8 (4.7 p.a.) |
|  | 160-179 | 247 | 21 | $85 \cdot 0$ (10.6 p.a.) |
|  | $180+$ | 167 | 20 | 119.1 (14.9 p.a.) |

TABLE VI. INCIDENCE OF CORONARY HEART DISEASE IN MALES IN RELATION TO DIASTOLIC BLOJD PRESSURE

| Age of <br> sample | Diastolic BP <br> $(\mathrm{mm} . \mathrm{Hg})$ | No. | CHD | Case <br> rate $/ 1,000$ |
| :---: | :---: | :---: | :---: | :---: |
| 40-54 years | Less than 75 | 109 | 2 | 18 |
|  | $75-84$ | 270 | 4 | 15 |
|  | $85-94$ | 209 | 4 | 20 |
|  | More than 95 | 99 | 7 | 71 |

In another study ${ }^{11}$ the WHO definition of hypertension is used, i.e. anyone with a systolic blood pressure above $160 \mathrm{~mm} . \mathrm{Hg}$ or diastolic blood pressure above $95 \mathrm{~mm} . \mathrm{Hg}$. The incidence of coronary heart disease, according to this definition of hypertension, is given for various ages, for the period 1950-1961, in rate per 1,000 in Table VII.

TABLE VII. INCIDENCE OF CORONARY HEART DISEASE IN RELATION TO BLOOD PRESSURE AND AGE

|  | Age-groups |  |  |
| :--- | :---: | :---: | :---: |
| Blood pressure | $40-49$ yrs | $50-59$ yrs | $60-69$ yrs |
| Normotensive | $75 \cdot 8$ | $200 \cdot 9$ | $209 \cdot 9$ |
| Hypertensive | $187 \cdot 5$ | $271 \cdot 2$ | $400 \cdot 0$ |

The enhanced risks of coronary heart disease in men with hypertension have been documented in nearly all the large prospective epidemiological studies in the USA and the UK. There can be no doubt that a consistent diastolic blood pressure of $95 \mathrm{~mm} . \mathrm{Hg}$ and above and a systolic pressure of $160 \mathrm{~mm} . \mathrm{Hg}$ and above at least double the risk of coronary heart disease.

## Combined Hypertension and Hypercholesterolaemia

The Framingham study ${ }^{12}$ has brought out the very greatly increased risk of coronary heart disease in subjects with both hypertension and a raised level of serum cholesterol. In men in the $45-60$-year age-group with a serum cholesterol of $225 \mathrm{mg} . / 100 \mathrm{ml}$. the incidence of coronary heart disease was $13 / 1,000 / 4$ years, whereas for those with a serum cholesterol level in excess of 260 mg ./ 100 ml . the incidence was $80 / 1,000$. In those with normal blood pressure the incidence was $17 / 1,000$ and in those with a diastolic blood pressure above $95 \mathrm{~mm} . \mathrm{Hg}$ the incidence was $100 / 1,000$. In the group that were normotensive and had serum cholesterol levels below 225 mg ./ 100 ml . the incidence was $10 / 1,000$. However, in the group that were hypertensive and had serum cholesterol levels above $260 \mathrm{mg} . / 100 \mathrm{ml}$. the incidence was 143/ 1,000 . The risk of developing coronary heart disease with both precursors was 14 times greater than in men with normal blood pressure and normal serum cholesterol levels.

## Smoking

A detailed report was given in 1964* of the relationship between cigarette smoking and the incidence of coronary heart disease in the Albany (New York) and Framingham (Massachusetts) studies. The populations studied were 2,282 middle-aged men under medical surveillance over a 10 year period in the Framingham study, and 1,838 men over an 8 -year period in the Albany study.
It was found that in men who smoked more than 20 cigarettes per day the risks of coronary heart disease were 3 times greater than in non-smokers, former smokers, and cigar and pipe smokers. No relationship was found between cigarette smoking and angina pectoris.

## Obesity

Kannel et al. in a report in $1967^{14}$ on the relationship between body-weight and the development of coronary heart disease in the Framingham study, examined the interrelationships between body-weight, serum cholesterol, blood pressure and the risks of developing coronary heart disease. There were 5,127 men studied over a 12 -year period.
The results showed that the level of antecedent weight, and a gain in weight, were strongly related to the risk of angina pectoris and sudden death which was not associated with thrombosis of coronary arteries. The excess risk of angina pectoris and sudden death appears to exist with and without elevation of blocd pressure and serum cholesterol, indicating an independent contribution of obesity to the development of these manifestations of coronary heart disease.

Subjects with obesity and hypertension and high serum cholesterol levels have a pronounced increase in the risks of sudden death, greater than that associated with each of the other factors alone. The data suggest that being overweight (i.e. more than $20 \%$ above the median for the weight and age) may be instrumental in bringing out the symptoms of angina pectoris, or in promoting sudden death, by imposing an increased work load on a heart with an already compromised coronary circulation.

## PREVENTION

Morris et al., in their paper in The Lancet in September $1966,{ }^{15}$ put the situation very well in this regard:
There is a new optimism that the modern epidemic of coronary heart disease of the middle-aged can be controlled. In the first place, investigators are adjusting themselves to the idea of "multiple" causes-their existence, how they connect and that conceivably there is no essential cause except perhaps for some threshold of nutrition which must be reached. Public health campaigns relating to these causes-e.g. the dangers of cigarette smoking and the need for sedentary men to take regular exercise-could be effective. But the dominant hope today is that action at the stage of the precursor pathology (hypertension and hypercholesterolaemia) may still achieve primary prevention. Individuals shown to be susceptible will be identified and prophylactic measures directed at them. Prevention will be translated into the clinical field.' (My italics.)

There is little doubt, from the points made earlier, that an annual examination of all males over the age of 40 years, at which body-weight, blood pressure and serum cholesterol are measured and smoking history and physical activities on and off the job are recorded, would serve to identify the individuals who have one or more percursors of coronary heart disease and have, therefore, a greater risk of coronary heart disease than normal. Once the susceptible individual has been identified he must have available the requisite preventive measures which will either halt the progress of the precursor pathology or reverse it. The following are, in brief summary, the preventive measures that should be provided:

1. Advice and assistance must be available from the individual's medical officer in: (i) planning a diet to reduce serum lipids for individuals of $40-50$ years of age with blood cholesterol values above $220 \mathrm{mg} . / 100 \mathrm{ml}$., and of 50 years and above with serum cholesterol values above $250 \mathrm{mg} . / 100 \mathrm{ml}$.; (ii) treatment of hypertension in individuals with diastolic blood pressures above $95 \mathrm{~mm} . \mathrm{Hg}$ and /or systolic blood pressures above $160 \mathrm{~mm} . \mathrm{Hg}$; (iii) stopping of smoking, especially if one of the above precursors of coronary heart disease is present.
2. There must be facilities for regular, daily exercise in congenial surroundings and under professional supervision as to the correct physical conditioning regimen to use and to ensure that no-one endangers his health.
It must be appreciated in this regard that recent research has shown that a game of tennis or 18 holes of golf over the weekend with no physical exercise during the week does not provide the level of physical activity which protects the individual from coronary heart disease. At least 30 minutes of regular, daily exercise is needed and this must be so designed that both submaximal endurance training and short, carefully controlled, maximal effort is included in the daily programme. The drawing up of a physical conditioning programme for middleaged men should be done on an individual basis and be regarded as a highly skilled task which can only be done satisfactorily, and with safety, by someone with a proper background in exercise physiology.
In regard to the use of exercise as a preventive measure against coronary heart disease there is today a considerable body of evidence in the medical literature on this subject. The present knowledge can be summarized as follows:

The probability of contracting coronary heart disease in the man who takes regular, daily exercise is much less than in the sedentary, inactive man, and, furtnermore, the chances of immediate death from coronary thrombosis are 3 times as great in sedentary, inactive individuals than in physically active persons. (It should be remembered that at present in $34 \%$ of cases of coronary thrombosis the patient dies immediately.)

It is not yet known how regular exercise protects the individual from coronary heart disease, or how the immediate fatality rate in coronary thrombosis is reduced by regular physical exercise, but there is some evidence that physical exercise leads to a better collateral arterial circulation. ${ }^{16}$ A thrombosis, except in one of the major coronary vessels, would not therefore cause as large an area of infarction of heart muscle in the physically active man as in the man with a poor collateral coronary artery circulation.

The effect of exercise on serum lipids and obesity appears to be the subject of controversy at present. This is probably due to the fact that some of the studies have been based upon physical conditioning programmes which are so mild, or so uncontrolled, as to be useless. Where a hard conditioning programme has been used, as by Carlson and Mossfeldt ${ }^{17}$ in their study in 1964, and by Holloszy et al. ${ }^{15}$ in 1964, a definite decrease in serum triglycerides has been shown but the effect on serum cholesterol is less certain, although Garrett et al. ${ }^{19}$ show a significant decrease in serum cholesterol after a ha:d physical conditioning programme.

The effects of exercise on blood pressure are also equivocal according to the scientific literature on the subject. However, the variation between workers in the physical conditioning programmes used might also be a factor in these equivocal results. Where a hard physical conditioning programme was used, as by Garrett et al.. a significant fall in diastolic blood pressure was recorded.

A number of researchers in this field have drawn attention to the improvement in the psychological attitude of the individual to his condition when he participates in a physical conditioning programme. A team spirit develops in the group undergoing physical conditioning and this has been found to be of very great benefit in sustaining the individuals in their difficult task of cutting down on saturated fats in the diet and in turning out regularly to carry out their exercises. Some researchers see the physical conditioning programme as the hub of the preventive measures and consider that the other measures should be built around the physical conditioning programme.

Scarcely a week goes by without some reference being made to the acute shortage in the Republic of trained and experienced men. It is in this group that the epidemic of coronary thrombosis takes its biggest toll. It is therefore in the interests of the State, and of business concerns, to see to it that every male above the age of 40 years is encouraged to seek a regular medical examination so that susceptible individuals with one or more precursors of coronary thrombosis are recognized as soon as the precursor pathology becomes manifest. Treatment of hypercholesterolaemia and hypertension is a matter for the individual's medical attendant. It is also in the interests of the State, and of industry and commerce, to provide. through existing physical educational institutes, and re-
search laboratories concerned with exercise physiology, the necessary facilities for regular, daily exercise under proper professional supervision. Only in this way is there some hope that the precursor pathology can be arrested and perhaps reversed. The costs of these facilities are small when seen in the context of the financial loss to the country each year of trained and experienced human material which cannot be replaced. One would like to see the Departments of Health and of Sport and Recreation give a strong lead on this important question, and the State and industry and commerce provide the funds for combating, on a national scale, this alarming epidemic.

## SUMMARY

Coronary heart disease has reached epidemic proportions in some western countries, including South Africa. In the USA the incidence in males is at least $760 / 100,000 /$ year and an appalling $35 \%$ die immediately in their first attack.

Physically inactive individuals have an early mortality which is 3 times that of active persons. The risks of coronary thrombosis are seriously increased if serum cholesterol levels exceed $250 \mathrm{mg} . / 100 \mathrm{ml}$., or the diastolic blood pressure is higher than $95 \mathrm{~mm} . \mathrm{Hg}$, or the systolic is higher than 160 $\mathrm{mm} . \mathrm{Hg}$. Individuals with both precursors have 14 times the risk of coronary heart disease compared with normal subjects. Obesity increases the risk of angina pectoris, and of sudden death which is not associated with thrombosis of coronary vessels.

The most important step in the prevention of coronary heart disease is the early recognition of precursor pathology by means of regular medical examinations of all persons over the age of 40 years. Treatment of hypercholesterolaemia and hypertension is a matter for the individual's medical attendant. Regular, daily exercise protects the individual from coronary heart disease. It is, therefore, in the interests of the State, and of industry and commerce, to provide the facilities for regular, daily exercise under proper professional supervision. Only in this way is there some hope that the precursor pathology can be prevented, or where it is present, that it can be arrested and perhaps reversed. The cost of these facilities is small when seen in the context of the financial loss to the Republic each year of essential, trained and experienced, manpower in its most productive period.

## REFERENCES

1. Raab, W. (1965): Med. Serv. J. Can., 21, 719.
2. Kannel, W. B., Kagan, A., Dawber, T. R. and Revotskie, N. (1962): Geriatrics. 17, 675 .
3. Morris, J. N.. Heady, J. A., Raffle, P. A. B., Roberts. C. G. and Parks, J. W. (1953): Lancet, 2, 1053 and i111.
4. Breslow, L. and Buell, P. (1960): J. Chron. Dis., 11, 421
5. Taylor, H. L.. Klepeter. E., Keys, A.. Parlin. W. Blackburn, H. Taylor, H. L., Klepeter. E.e. Keys. A. Parlin. W. .
and Puchner, T. (1962): Amer. J. Publ. Hith, 52, 1697.
6. Kahn, H. A. (1963): Ibid., 53, 1058.
7. Frank, C. W., Weinblatt, E., Shapiro, S. and Segar, R. V. (1966): Circulation, 34, 1022.
8. Keys, A. and Blackburn. H. (1963): Progr. Cardiovasc. Dis., 8, 14
9. Jolliffe, N. (1959): Circulation, 20, 109.
10. Chapman, J. M., Goerke. L. S., Loveland, D. B. and Philips, E. (1957): Amer. J. Publ. Hith, 47, 33.
11. Chapman. J. M. and Massey. F. J. (1964): J. Chron. Dis., 17. 933
12. Kannel, W. B., Dawber. T. R.. Kagan, A.. Revotskie. N. and Stokes, J. (1961): Ann. Intern. Med., 55, 33.
13. Doyle, J. T. Dawber. T. R.. Kannel. W. B... Kinch, S. H. and Kahn. H. (1964): J. Amer. Med. Assoc., 190, 886.
14. Kannel, W. B., Lebauer, E. J.. Dawber, T. R. and McNamara, P. M. (1967): Circulation, 35, 734.
15. Morris, J. M.. Kagan, A., Pattison. D. C., Gardiner, M. J. and Raffe, P. A. B. (1966): Lancet, 2, 553.
16. Eckstein. R. W. (1957): Circulat. Res., 5, 230.
17. Carlson, A. L. and Mossfeldt, F. (1964): Acta. physiol. scand. 62. 51.
18. Holloszy, J. O., Skinner, J. S. Toro, G. and Cureton, T. K. (1964): Amer. J. Cardiol., 14. 753.
19. Garrett. H. I., Pangle, R. V. and Mann, G. V. (1966): J. Chron
