It was of course impossible to compare this selected series of hypertensive women with any normal population, and we therefore converted their blood pressures into scores adjusted for age according to the method of Hamilton, Pickering, Fraser Roberts, and Sowry (1954b). By this method any blood pressure can be converted into a corresponding pressure at the age of 60, so that pressures at all ages can be compared. For instance, at the age of 35 the average diastolic pressure for a woman is 80. If her diastolic pressure is in fact 100, or 20 mm. above the average, she scores, not +20, but +25, because, owing to the curve for age, her blood pressure at 60 will probably be 25 mm. above average. A woman of 20 with a diastolic pressure of 100 would, however, score +55 on the same scale, whereas a woman of 45 with a diastolic pressure of 100 would score only +15. This seemed to us to be the only way of trying to make a comparison between the starting pressures of these hypertensive women and their blood pressures recorded about four years later.

The variations from case to case in this series are enormously greater than those in the toxæmic series. Some women with quite high blood pressures seem to be completely unaffected by the pregnancy—in fact, the follow-up pressure may even be lower than the initial one. In other cases extreme rises of pressure are found; for instance, from 140/90 in a woman of 42, to 220/140 five years later. Until we know more about the factors concerned in the development and progression of hypertension, it is somewhat doubtful whether the comparison made here has much validity, but, for what it is worth, the average score for starting systolic pressure was +51; at the follow-up this had increased by 17. The score for the initial diastolic pressure was +25, and this had increased by 8 at the follow-up examination. Translating this back into real blood pressures—for instance, in a woman aged 40—an initial pressure of about 165/100 would be converted into one of 180/110; as the effect of age is eliminated this would seem to be a significant increase attributable entirely to the pregnancy, but again let us remark that fluctuations between individuals are extreme, and there is comparatively little correlation between the height of the starting pressure and the gain of pressure which may be anticipated.

Comment

Although we believe that this paper brings to light some facts about the late prognosis of pregnancy toxæmia which have not been previously shown so clearly, it has to be admitted that the evidence could be challenged on at least two points. The first is that the initial pressure and the follow-up pressure were in most cases not recorded by the same person. If this were a serious source of inaccuracy we do not think the records would show such a clear similarity between the initial pressures and the pressures recorded in the London series for the same age groups; neither do we think that it would show such a regular shift to the right in the follow-up pressures of all age groups. The second point is that we have used as our controls the records of blood pressures from an unselected population—that is, the London series. The ideal control would have been a series of women who had passed through a non-toxæmic pregnancy.

Summary and Conclusions

Further consideration of a previously recorded series of 446 cases of pre-eclamptic toxæmia in women whose blood pressure early in pregnancy was normal clearly

shows that their mean blood pressures approximately four years after the toxæmic pregnancy are much higher than the mean pressures which would be expected in an unselected population of women of similar age. Nevertheless, severe hypertension is a rare sequel of toxæmic pregnancy in a woman previously normotensive. Similarly, in women who had toxæmic pregnancies superimposed on hypertension the rise of blood pressure on re-examination was more than could be accounted for by an increase of age of approximately four to five years.

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ISCHAEMIC ELECTROCARDIOGRAMS IN SYMPTOMLESS MEN

WITH A NOTE ON THE SERUM LIPOPROTEINS

BY

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Much reliance is placed on the electrocardiogram (E.C.G.) in the diagnosis of ischaemic heart disease, especially in cases where the pain is atypical. Most physicians would be prepared to disregard a normal tracing in a patient with a classical history of effort pain or with clinical manifestations of myocardial infarction; but when these features are equivocal their interpretation is apt to be influenced by the electrocardiographic findings. While this approach is usually justified, the wording of some requests for electrocardiography ("Chest pain . . . ? evidence of ischaemia") at least conveys the impression that the tracing is to be used as a diagnostic arbiter, on the thesis that chest pain with an abnormal E.C.G. is necessarily cardiac pain. It should, however, be remembered that coronary artery disease is commonly found at necropsy when there have been no referable symptoms during life, and it is therefore debatable whether electrocardiographic evidence of myocardial ischaemia can invariably be equated with clinical manifestations. Hence, to assess the reliability of the E.C.G. in diagnosis it is important to know how often an ischaemic tracing may be a chance finding.

The literature contains several reports of such tracings being recorded in subjects without chest pain. The significance of many of these series is questionable, either because cases of hypertension or valvular disease (which produce similar electrocardiographic abnormalities) were included, or because insufficient leads were recorded. Using full leads in clinically healthy subjects, Wosika *et al.* (1950) noted ischaemic tracings in 21% of people over 80, and Acheson (1957) noted them in 10% of R.A.F. personnel aged between 19 and 54.

However, the maximum incidence of coronary artery disease is in men in their fifties and sixties (Peel, 1955)—that is, between the age groups covered by the above two series. It is therefore among these that the assessment of chest pain assumes most importance. We have investigated the incidence of ischaemic E.C.G.s in men without chest pain in the age group 50 to 80, adopting rigorous criteria to exclude other causes of electrocardiographic abnormality.

The association between abnormalities in the serum lipoproteins and coronary atheroma (Gofman *et al.*, 1950; Jones *et al.*, 1951) has been the subject of much discussion in recent years (for review, see Oliver and Boyd, 1957); consequently we also studied the serum lipoproteins in these men and compared them with cases of coronary disease.

Method

The subjects studied were 100 male hospital in-patients, aged at least 50, who conformed to the following criteria: (1) no chest pain, or history thereof, or shoulder pain; (2) no evidence of valvular or any other type of heart disease, or heart failure, or pericarditis; (3) diastolic blood pressure not greater than 90 mm. Hg; (4) no cardiac enlargement on x-ray film; (5) no renal or endocrine disorder capable of producing major electrolyte disturbance; (6) no diabetes; (7) no syphilis; (8) serum cholesterol under 300 mg./100 ml.; (9) no evidence of peripheral or cerebral vascular disease; (10) no arrhythmia other than ectopic beats. Other causes of electrocardiographic abnormality were excluded by criteria 2 to 5; and conditions with a high incidence of coronary disease were excluded by criteria 6 to 9.

The conditions which had caused admission to hospital are listed in Table I. Fifty-seven of the men were aged 50 to 59, 26 were 60 to 69, and 17 were 70 to 80. Each was questioned and examined clinically by

one of us (D.W.) and by at least one other medical officer. A 6-foot (183-cm.) chest film was taken for heart size. A 12-lead E.C.G. (I, II, III, AVR, AVL, AVF, V_1 - V_6) was recorded at rest. The subject was then exercised (unless unfit) by running or walking briskly up several flights of steps, stopping at his own request. Thirty patients were not fit for exercise. After exercise, leads V_5 and V_6 were repeated at two-minute intervals for 10 minutes.

We used the usual criteria for electrocardiographic evidence of myocardial ischaemia: large Q waves, flattening or inversion of T waves, and depression of the ST segment at rest or after exercise. Although such ST and T changes are not specific, and can be produced by ventricular hypertrophy, pericarditis, and electrolyte disturbances, the selection of cases ensured the exclusion of such causes. Flattening of the T waves alone or ST depression of less than 1 mm. was not accepted as evidence of ischaemia unless square depression of the ST segment of greater amplitude followed exercise; if no change occurred the tracings were regarded as equivocal and were not included in the ischaemic total. The changes induced by exercise were assessed when the heart rate had returned to the resting figure.

Since the investigation was begun 35 men have died as a result of the illnesses which occasioned the original admission. Necropsy was performed in 19 who died in hospital, and in 12 of these the coronary arteries were examined radiographically after injection of a suspension of bismuth oxychloride. The technique was similar to that described by Shillingford (1950). The survivors are being seen annually for clinical examination, electrocardiography, and lipoprotein study; so far 29 have been followed for up to three years.

Results

The electrocardiographic findings are shown in Table II. Abnormal tracings were recorded from 12 patients; examples are shown in Figs 1-4. Since none of these men had any serious electrolyte disturbance, pericarditis, or any lesion causing ventricular strain, the ST and T wave abnormalities were interpreted as due to myocardial ischaemia. Three more tracings showed right bundle-branch block: as this may be a

TABLE I.—Diseases in the 100 Cases Investigated

Diagnosis	No. of Cases	Diagnosis	No. of Cases
Peptic ulcer	30	Disseminated sclerosis ..	1
Neoplastic lesions ..	29	Malignant exophthalmos ..	1
Respiratory infections ..	8	Trigeminal neuralgia ..	1
Reticulosis	6	Senile osteoporosis ..	1
Cirrhosis hepatis ..	4	Herpes zoster	1
Disk prolapse	3	Cholecystitis	1
Intestinal infections ..	3	Investigations negative or inconclusive ..	9
Rheumatoid arthritis ..	1		
Dermatomyositis	1

FIG. 1

FIG. 2

FIG. 3

FIG. 1.—Ischaemic pattern in leads I, II, L, V_1 , and V_6 . FIG. 2.—Anterior (intramural) infarction. FIG. 3.—Posterior infarction.

congenital abnormality they were excluded from the ischaemic total, as were another three that showed ischaemic changes at low haemoglobin levels but became normal after treatment of the anaemia. Ischaemic tracings were recorded in four men aged 50-59, four aged 60-69, and four aged 70 and over.

FIG. 4.—Lead V, two minutes after exercise test. Annual tracings with change from a normal to an ischaemic pattern. There was no pain on exercise, and the man has remained symptom-free with unimpaired effort tolerance.

TABLE II.—*Electrocardiographic Findings in 100 Men Without Chest Pain or Evidence of Heart Disease*

Ischaemic	12
Infarction	2
ST segment and T waves abnormal at rest	8
Normal at rest, ST segment and T waves abnormal after effort	2
Abnormals not included in ischaemic total	12
Right bundle-branch block	3
Abnormal during anaemia, normal after treatment	3
Equivocal	6
Normal at rest and after effort	76

Of the 19 cases that later came to necropsy, six had had ischaemic E.C.G.s during life. In all 19 the absence of any cardiac lesion, other than coronary atheroma, was confirmed. In 12, including three with ischaemic E.C.G.s, the coronary arteries were examined radiographically, after injection of bismuth oxychloride in gelatin. Evidence of significant abnormality, sufficient to cause myocardial ischaemia, was sought, using two criteria: (1) an increase in the number of small anastomotic vessels (Shillingford, 1950); and (2) development of a subendocardial plexus, as described by Fulton (1956).

A normal vascular pattern was demonstrated in six cases (Fig. 5), all with normal E.C.G.s. An increased anastomotic pattern, with a subendocardial plexus

FIG. 5.—Normal coronary arterial pattern. From a man of 73 with a normal E.C.G.

FIG. 6.—Extensive small-artery anastomotic pattern. From a man of 53 with an ischaemic E.C.G. but no chest pain.

indicative of ischaemia, was found in the remaining six, of whom three had ischaemic E.C.G.s: in these three the anastomotic network was particularly dense (Fig. 6).

Discussion

Before accepting that the abnormal tracings were caused by myocardial ischaemia, all other factors must be considered. ST segment and T-wave changes produced by ventricular hypertrophy, pericarditis, and electrolyte disturbance (particularly hypokalaemia) were excluded by selection of cases; the absence of cardiac lesions was confirmed at necropsy. Right bundle-branch block and transient changes from anaemia have not been included in the ischaemic total. Other possibilities to be taken into account are the effects of age, extracardiac disorders, and physiological factors.

The effect of age alone cannot be assessed during life, since coronary atheroma cannot be excluded. Olbrich and Woodford-Williams (1953) found the only changes constantly attributable to age were increased duration of the QRS complex and diminished amplitude of T waves in the precordial leads. We have not included such minor deviations in our ischaemic total. Silver and Landowne (1953) noted depression of ST segments of up to 1.5 mm. after exercise in the aged; this might well be due to ischaemia.

Diseases of other organs are known sometimes to produce transient inversion of T waves, and Levine (1953) lists, among other causes, shock, anoxia, carbon monoxide poisoning, pulmonary embolism, acute infections, intracranial diseases, and endocrine disorders. In our series these conditions were excluded, and the patients with acute infections were studied after recovery.

Physiological alterations of the E.C.G. resembling those due to coronary disease may be produced by

meals (Gardberg and Olsen, 1939; Simonson and Keys, 1950), by emotional disturbance and by smoking (Gardberg and Rosen, 1957; Rosen and Gardberg, 1957), and by respiration (Gazes, 1950; August *et al.*, 1958). Rochlin and Edwards (1954) attribute this effect of meals to redistribution of potassium consequent upon carbohydrate absorption, and consider that only a large carbohydrate meal would be likely to produce such effects. Our tracings were usually recorded before meals, or after a small amount of food only. Gardberg and Rosen (1957) attribute ST and T changes induced by exercise, emotion, or smoking in healthy subjects to an alteration in the gradient of repolarization from tachycardia. In our series such changes were not assessed during tachycardia. Respiratory variations are recognizable by cyclic variations in the tracing, and these have been allowed for in assessing our results. In addition, the abnormal pattern has persisted in the cases followed annually so far, which is against transient physiological alterations. Furthermore, at necropsy the cases with abnormal E.C.G.s were found to show the vascular pattern associated with myocardial ischaemia (Shillingford, 1950; Fulton, 1956), and the absence of other pathological causes was confirmed.

Taking all the evidence into consideration, we conclude that the electrocardiographic abnormalities found in our cases represent myocardial ischaemia without referable symptoms or other signs. It is well known that coronary atheroma, with narrowing, occlusion, and myocardial fibrosis, are not uncommonly found at necropsy in this age-and-sex group when there have been no symptoms during life; it is not surprising that this is also occasionally reflected by the E.C.G. Our figure of 12% is similar to that of 10% found by Acheson (1957) in younger men; and it has been shown that marked coronary atheroma can be found from the age of 20 in men of Western races (Enos *et al.*, 1955).

Our findings therefore confirm that abnormal E.C.G.s due to myocardial ischaemia are not rare among middle-aged men without cardiac pain. It follows that the recording of an ischaemic tracing in a patient with chest pain does not inevitably mean that the pain is of cardiac origin. In cases of hiatus hernia or spinal disease an abnormal tracing could well mislead the physician. This re-emphasizes the necessity for careful assessment of the history and clinical data in all cases of chest pain. As stated earlier, patients with normal E.C.G.s may none the less be correctly regarded as cases of ischaemic heart disease because of other relevant considerations. The clinician should similarly feel free to exercise his judgment when the E.C.G. is abnormal in a patient whose pain is not really suggestive of a cardiac origin. To quote East (1950): "The cardiogram is only one detail in the clinical picture—its importance can be assessed only by seeing the picture as a whole."

Serum Lipoproteins

The serum lipoproteins were studied in 59 patients, of whom nine had ischaemic E.C.G.s. The method used was paper electrophoresis as described by Dangerfield and Smith (1955). They observed an abnormal band migrating ahead of beta-lipoprotein (Fig. 7) in most patients with myocardial infarction. Subsequent studies on larger series of patients have confirmed the associa-

tion of this "pre-beta-lipid" band with myocardial infarction (Besterman, 1957; Smith, 1957), and it has been demonstrated by Smith (1957) that it is roughly equivalent to the ultracentrifugal Sf 20-100 group of Gofman *et al.* In this investigation the presence of moderate or large amounts of the pre-beta-lipid band

FIG. 7.—Electrophoretic patterns given by serum (a) from a normal woman, and (b) from a patient five weeks after myocardial infarction. P., part of strip stained for protein; L., part of strip stained for lipid; alb., albumin; α-L.P., alpha-lipoprotein; β-L.P., beta-lipoprotein; P.-β-L., pre-beta-lipid.

was used as the criterion of lipoprotein abnormality. The band was assessed quantitatively by the score system described by Smith (1957) and divided arbitrarily into three categories—minimal (score 0-1½), moderate (score 2-4), and large (score 4½-7).

The lipoprotein findings were compared with those in two other groups of men within the age range 50-70: 71 with known ischaemic heart disease and 104 in apparent good health. These last two groups have previously been reported by Smith (1957). They were compared also with the distribution of the pre-beta-lipid band in 232 healthy men aged 20-84.

Results

The type of lipoprotein abnormality looked for is illustrated in Fig. 7. The prevalence of minimal (score 0-1½), moderate (score 2-4), and large (score 4½-7) pre-beta-lipid bands in the 59 hospital in-patients without chest pain is shown in Table III, and compared with cases of established ischaemic heart disease and with healthy men in the same age range. A moderate pre-beta-lipid was found in approximately half of each group. A large pre-beta-lipid band was found in 10%

TABLE III.—Pre-beta-lipid Level in Various Groups of Patients

	Group of Patients	No.	Aver. Age	Pre-Beta-Lipid Level			
				Aver. P.-β-L.	Min.	Mod.	Large
Patients in electrocardiographic series	Normal E.C.G.	50	60	2.5	36%	54%	10%
	Ischaemic	9	63	3.8	11%	55%	33%
Patients with coronary disease	Acute myocardial infarction examined within 3 months of the attack* ..	43	59½	4.0	7%	51%	42%
	Angina with no history of infarction	28	59	3.6	7%	57%	36%
Controls	Healthy men aged 50-69 ..	104	60	1.5	53%	44%	3%

* From Smith (1957).

or less of the hospital patients with no pain and normal E.C.G.s, and in the healthy men; it occurred in 33% of the patients without pain but with ischaemic E.C.G.s, a figure comparable to the 36-42% in established cases of cardiac infarction and angina.

Discussion

To provide a standard of comparison against which the lipoprotein findings can be assessed, the distribution of the pre-beta-band in 232 healthy men aged 20-84 years is shown in Fig. 8; this shows the average

FIG. 8.—The pre-beta-lipid level in healthy men of different ages. The histogram shows the distribution of minimal, moderate, and large pre-beta-lipid bands in successive decades, and the graph shows the average pre-beta-lipid score.

pre-beta-lipid score and the percentage with minimal, moderate, and large pre-beta-lipid bands in different decades. There is marked variation with age, and, although the lipoprotein pattern is normal in 80% of men in their twenties, a moderate pre-beta-lipid is found in over 60% of men in their fifties; a large pre-beta-lipid is, however, very rare in healthy men of any age, and was found in only six (2½%) out of the whole group.

An examination of the results in Table III suggests a number of points. Firstly, a moderate or large pre-beta-lipid was found rather more often in the hospital patients with normal E.C.G.s than in healthy men of comparable age. We have observed a large pre-beta-lipid band in a number of unrelated conditions, including dermatomyositis, gastric ulcer, carcinoma of the bronchus, carcinoma of the bladder, and pulmonary tuberculosis, but the findings are not consistent; it seems probable that where there is marked metabolic disturbance the lipoprotein patterns may also be disturbed, and this must be borne in mind in their interpretation. Secondly, a moderate pre-beta-lipid band occurs in about half the men in every group; thus, although it may have some significance in relation to atheroma, its presence does not correlate with clinical coronary disease. Thirdly, a large pre-beta-lipid band occurs in about one-third of patients with electrocardiographic evidence of myocardial ischaemia whether or not there be referable symptoms, although the symptomless group is not really large enough for comparison. Considering this finding in relation to

Smith's (1957) observation of a striking increase in pre-beta-lipid after myocardial infarction, we are tempted to speculate whether a large pre-beta-lipid band (roughly equivalent to the Sf 20-100 group of Gofman *et al.*) may be associated with myocardial damage rather than with coronary atherosclerosis.

We intend to continue to follow up the surviving patients in the group without chest pain and to report further on any subsequent development of clinical coronary disease in relation to the electrocardiographic and lipoprotein findings.

Summary

Electrocardiograms were recorded in 100 men aged between 50 and 80 years, none of whom had chest pain or any evidence of cardiac disease. Twelve tracings showed evidence of myocardial ischaemia. This emphasizes the need for care in using electrocardiography in the assessment of chest pain, which is not necessarily of cardiac origin even though the tracing be abnormal.

In 59 of these men, including nine with abnormal tracings, the serum lipoproteins were examined by paper electrophoresis for the presence of an abnormal pre-beta-lipid band (which corresponds approximately with the Sf 20-100 fraction of Gofman *et al.*). The results were compared with those in known cases of ischaemic heart disease. A moderate quantity of abnormal lipid was found in a similar percentage of both groups and did not correlate with clinical coronary disease. A large abnormal band did, however, appear to correlate with electrocardiographic evidence of myocardial ischaemia.

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