felt tired, one had visual hallucinations of coloured lights on this dose. This latter side-effect also occurred after five weeks on 100 mg. q.d.s. These side-effects were all readily relieved by reducing the dose. Two of the hypertensive anginal patients on 400 mg. daily have not experienced any side-effects: we have not increased the dose above this level.

Discussion

Fifteen out of 16 hypertensive patients given propranolol for up to seven months have shown reductions of blood-pressure. Propranolol alone may prove to be useful in the treatment of mild and moderately severe cases of hypertension. In one patient experiencing marked drowsiness on methyldopa a change to propranolol resulted in improved blood-pressure control with no side-effects. Propranolol produced a considerable hypotensive effect in patients on adrenergic neurone-blocking and milder hypotensive drugs.

Propranolol has so far proved relatively free from side-effects and patients usually feel well on the drug. We have seen one case where heart failure was precipitated by propranolol; this has been reported following pronethalol (Stock and Dale, 1963). We consider that propranolol should be used with great caution, if at all, in patients with a history suggestive of heart failure, though one such patient with severe angina responded well without trouble. The only other side-effect in the dosage recommended for the treatment of hypertension, up to 200 mg. a day in divided dosage, has been slight tiredness in 2 of the 23 patients, readily relieved by reduction of the dosage. The side-effects seen with larger doses used in our angina trial have also been relieved by reducing the dose.

While a central mode of action is not excluded it is suggested that beta-receptor-blocking drugs exert their hypotensive action by blocking the sympathetic receptors in the heart. A feature of both pronethalol (Prichard, 1964) and propanolol (Tables I and II) has been the absence of postural hypotension. In all of the 14 patients (Cases 1–7, 17–23) receiving propranolol alone there is a rise or no change in the diastolic pressure on standing. This would be expected, as the response of the cardiovascular system to the effect of gravity is chiefly mediated by increasing sympathetic (alpha) vasoconstrictor tone.

Pronethalol given intravenously does not exert any significant effect on the blood-pressure (Dornhorst and Robinson, 1962; Prichard, 1964) and our preliminary results suggest that the closely related drug propranolol also has no effect (Hodge and Prichard, unpublished data). Pronethalol immediately modifies cardiovascular responses, as shown by its reduction of the cardiac response in Valsalva's manœuvre (Prichard, 1964); it reduces the reflex tachycardia during effort and the pulse pressure in overshoot, and preliminary experiments suggest (Hodge and Prichard, unpublished data) that propranolol has a similar action. While beta-receptor-blocking drugs have no hypotensive action following intravenous administration there is a slight hypotensive effect after short-term oral use of pronethalol (two to four weeks, Prichard, 1964; one week, Schröder and Werko, 1964). A considerable response has been obtained when either pronethalol or propranolol has been given for a prolonged period.

The tentative suggestion is made that these drugs act by reducing the cardiac response to stimuli which may be responsible for transient rises in blood-pressure. This is suggested by the modification of Valsalva's manœuvre. This damping-down of pressor responses may gradually condition the baroceptors to regulate the blood-pressure at a lower level in hypertensive and normotensive patients. However, the response to acute cardiovascular demands involving largely alterations in vascular tone is relatively unimpaired; this is manifest in the response to exercise and posture in patients receiving propranolol.

Initial studies suggest that propranolol has a useful hypotensive action, worthy of further study. It is relatively free from side-effects in the recommended dosage for hypertension.

Summary

Propranolol (Inderal) has been given to 24 patients, 16 of whom were hypertensives. Therapy was stopped in one patient after two days, as heart failure developed, otherwise it is relatively free from side-effects in the dosage recommended for hypertension.

Alone or in combination with other drugs it exerts a considerable hypotensive action in hypertensive and normotensive patients.

It is thought propranolol may exert its hypotensive action by interfering with the function of sympathetic nerves to the heart.

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Glucose-tolerance Test in Hypertensive Patients

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Brit. med. J., 1964, **2**, 727–730

The association between diabetes and coronary artery disease is well recognized, and recently a high proportion of patients with coronary disease have been shown to have disturbed glucose-tolerance tests (Sowton, 1962) or increased insulin antagonism (Vallance-Owen and Ashton, 1963).

It is noteworthy also that even in the absence of glycosuria 14.5% of apparently normal subjects over the age of 50 years reported in the College of General Practitioners' survey (1963) had abnormal glucose-tolerance curves. It would be surprising if hypertensive patients, not necessarily suffering from overt diabetes, did not also show a proportion with abnormal glucose-tolerance tests, and in view of the findings of Vallance-Owen and Ashton and of Sowton it is clearly important to establish the relationship between the two conditions.

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The present study attempts to define, in a number of hypertensive patients, the relationship between coronary artery disease and diabetic status, as judged by the oral glucose-tolerance test.

Method

The only requirement for inclusion in the survey was that the patient must have been accepted for treatment at the Dunedin Hypertension Clinic. There were 107 patients, 46 men and 61 women.

Patients were questioned in detail as to the presence of angina or other coronary manifestation past or present, this being amplified by reference to the patient's case notes. On the result of this assessment the patient was assigned to one of four categories: (1) cardiac infarction ; (2) definite angina ; (3) possible angina ; (4) no symptoms of coronary disease. In those patients in the "cardiac infarction" category the glucose-tolerance test was carried out on the male patients between six months and eight years (mean 2.6 years) after the coronary episode, in the female patients four months to six years (mean 2.0 years) later.

A 12-lead electrocardiograph was carried out, and, where possible, precordial leads V4-V6 were repeated immediately after exercise and at two and four minutes after exercise.

A modified glucose-tolerance test was carried out after an all-night fast and the precaution taken of ensuring that no patient had been on a reducing diet before the test. Venous blood was sampled in the fasting condition and one and two hours after a 100-g. glucose load. Blood-sugar determinations were made using the Somogyi-Neilson method.

Selection was employed so as to include a reasonable number of patients in each of the main categories, but there was no conscious selection within a category. In the case of the cardiac-infarct group the relatively small number of patients with this complication demanded that every available patient be seen over the period of study.

Results

Glucose-tolerance Test

Diabetes was known to exist in three of the patients studied.

Interpretation of the modified glucose-tolerance test was based on an adaptation of the criteria of Conn and Fajans (1961) whereby a result is considered abnormal if the one-hour blood-glucose level is 160 mg. or greater and the two-hour level is 120 mg. or greater. It is emphasized that the use of venous blood would tend to give levels of blood sugar 10–20 mg.% lower than those obtained for capillary blood, a circumstance operating against "over-diagnosis" since the criteria of Conn and Fajans (1961) refer to studies using capillary blood.

Table I shows the group of patients studied divided on the basis of the result of the glucose-tolerance test. The mean ages and standard deviations of the males and females in each clinical category are given. The age difference between the two major categories of 2.1 years is not statistically significant ($0.2<P<0.3$).

Comparison of the incidence of abnormal glucose tolerance between those patients with objective evidence of ischaemic disease, or angina, and those without evidence shows a significant excess of affected patients in the "positive glucose-tolerance test" group on application of the χ^2 test ($0.025<P<0.05$).

Examination of the data in Table I relating to the patients having "possible angina" and patients without evidence of coronary artery disease shows that there is significant excess of patients with abnormal glucose tolerance ($0.02<P<0.05$) in the former category.

Table II compares the actual blood-glucose values obtained during the performance of the glucose-tolerance test of the patients with an accepted history of a previous cardiac infarct and those without symptomatic evidence of coronary disease. The higher blood-sugar values in this coronary group differ significantly from the "no symptoms" group on analysis of variance ($P<0.001$).

TABLE II.—*Blood-sugar Levels Obtained During Modified Glucose-tolerance Tests in Two Groups of Patients, With Documented History of Infarct and Without Symptoms of Coronary Artery Disease*

	No.	Blood-sugar Levels		
		Fasting	One Hour	Two Hours
No coronary symptoms ..	36	80·9	135·4	111·3
Known infarct	22*	90·59	155·5	126·1

* One patient, a previously diagnosed severe diabetic, was not retested and his figures were not incorporated in this Table.

Basal Blood-pressure

Basal blood-pressure values, which had been determined before starting treatment, were available in all but two of the 107 patients studied. The results are summarized in Table III. No marked difference in pressure between the groups is noted apart from the systolic readings for the female patients in the "cardiac infarct" and "angina" groups and the male patients in the "possible angina" and "no symptoms" categories where differences of 12.2 and 14.2 mm. Hg are noted respectively. In neither case are the differences statistically significant.

TABLE I.—*Sex and Age of Patients Defined According to Detailed Assessment of Evidence of Coronary Artery Disease and Shown Relative to Result of Glucose-tolerance Test*

Clinical Category	Total	Sex	Glucose-tolerance Test							
			Positive				Negative			
			No.	Mean Age	SD	Total	No.	Mean Age	SD	Total
Objective evidence of ischaemic disease	53	M	7	59·3	6·2	18	17	57·7	8·6	35
		F	11	60·1	6·6	62%	18	60·2	6·6	45%
Angina without objective evidence of ischaemic disease	10	M	1	62·0	—	4	—	—	—	6
		F	3	63·3	4·9	14%	6	62·3	6·3	8%
Possible angina	16	M	—	—	—	5	6	52·9	5·3	11
		F	5	62·4	9·3	17%	5	60·8	6·4	14%
No angina or ischaemic E.C.G. changes	28	M	1	58·0	—	2	14	56·1	6·2	26
		F	1	51·0	—	7%	12	57·6	8·8	33%
Mean of males plus females	107			60·3		29 100%		58·2		78 100%

TABLE III.—*Basal Blood-pressure Levels*

	Cardiac Infarct (23*)		Angina (26)		Possible Angina (21)		No Coronary Symptoms (35*)	
	M (11)	F (12)	M (6)	F (20)	M (9)	F (12)	M (18)	F (17)
Mean systolic mm. Hg	152·0 s = 19·9	155·0 s = 17·9	149·0 s = 36·9	167·2 s = 28·6	162·4 s = 30·4	163·7 s = 21·8	148·2 s = 28·1	157·5 s = 29·3
Mean diastolic mm. Hg	99·1 s = 15·2	96·8 s = 14·4	92·2 s = 15·7	96·3 s = 13·4	100·4 s = 17·2	94·2 s = 10·3	90·7 s = 17·5	100·1 s = 19·2

* These figures differ from those in Table I owing to absence of basal blood-pressure values in two patients.

Electrocardiography *

All patients in the study had a 12-lead resting electrocardiograph, and a recording was also obtained after exercise in all but eight patients. The tracings were separately assessed by two observers who did not know the patient's name or medical history. Particular attention was paid to the presence of abnormal Q waves, T-wave depression, high voltages, ST-segment depression of 1 mm. or more after exercise, and T-wave changes after exercise. Complete agreement was obtained between the two observers in about 70 of the tracings. In cases where some disagreement was found the traces were reassessed. By limiting assessment to the presence or absence of certain changes the subjective element was reduced to a minimum.

Seven patients with pathological Q waves and positive glucose-tolerance tests were found ; two of these were patients with no documented history of infarct. The relationship of the E.C.G. findings to the glucose-tolerance test is shown in Table IV. The number of patients with abnormal Q waves in the group of patients with impaired glucose tolerance did not exceed the expected value at a significance level of 5%.

TABLE IV.—*E.C.G. Features in* 107 *Patients Shown Relative to Results of Oral Glucose-tolerance Test*

Glucose-tolerance Test	Abnormal Q Waves		T-wave Changes Only		Remainder		Total
	No.	Expected Values	No.	Expected Values	No.	Expected Values	
Positive ..	7	5·3	7	8·2	15	15·5	29
Negative ..	12	13·7	38	36·8	28	27·5	78
Total ..	19		45		43		107

Exercise Test

Thirty patients showed ST-segment depression of 1 mm. or more in records from E.C.G. leads V4 to V6 after varying degrees of effort. Nineteen of these patients had other evidence of ischaemic heart disease either in their clinical history or on the basis of other E.C.G. findings. In the 11 patients, five males and six females, with ST-segment depression without other evidence of ischaemic disease there were four (36%) with "positive" glucose-tolerance curves. Of patients with negative histories and E.C.G.s free of evidence of ischaemic disease there were 44 who did not have ST-segment depression after effort ; only seven of these (16%) had "positive" glucose-tolerance tests. This finding is in accord with the other evidence in this survey, linking ischaemic heart disease and impaired glucose tolerance.

Coronary Artery Disease and Thiazide Diuretic Drugs

Seventy-five of the patients in the study group had been receiving thiazide diuretics for six months or longer. The incidence of coronary artery disease, with E.C.G. changes, or based on an accepted history of angina pectoris as compared with patients without symptoms, or chest pain not acceptable as angina, did not differ significantly between patients who were or were not on long-term thiazide therapy ($\chi^2 = 1.58$, $0.6 < P < 0.7$).

Discussion

The high incidence of coronary artery disease in affluent societies has prompted prospective studies (Dawber *et al.*, 1962) which attempt to define certain factors common to individuals who develop ischaemic heart disease, but abnormalities of glucose tolerance have not been emphasized in these reports.

Because of the method of selection employed in the present study, random with respect to patients within the groups defined but not random with respect to the clinic population as a whole, comparisons can be made between the groups but not relative to the clinic population as a whole.

Of particular interest is the finding in the coronary group, judged on past history and E.C.G. findings, but not on the resting E.C.G. alone, of impaired glucose tolerance. The high incidence of coronary artery disease in florid diabetes is well known, but most of the abnormalities of glucose tolerance recorded in this investigation were only detected as a result of an oral glucose-tolerance test and usually in the presence of a normal or near normal fasting blood sugar—the type of abnormality described by White (1962) as "chemical diabetes." Sowton (1962) noted abnormal glucose-tolerance tests in 73% of the 30 patients who were tested immediately after infarction, and three years after infarction four out of 15 patients had abnormal curves. Vallance-Owen and Ashton (1963) likewise found increased serum-insulin antagonism in patients with coronary thrombosis and considered that many patients with this disorder were essential diabetics only rarely showing carbohydrate intolerance.

If the reported data are considered it is seen that 35% of our patients with accepted evidence of ischaemic heart disease had positive glucose-tolerance curves compared to 16% of positive tests in patients with doubtful or no symptomatic evidence of coronary disease. The observation prompts the inquiry as to the part played by the widely used thiazide diuretics in "exposing" latent diabetics (Shapiro *et al.*, 1961) and perhaps increasing the coronary hazard. Examination of case records showed, however, that there was no significant difference in the incidence of coronary disease between patients who were or were not on thiazide diuretics. It would thus seem unlikely that thiazides influence the incidence of cardiac infarction if one excepts the remote possibility that if thiazides were responsible for a high incidence of fatal thrombosis the association need not be apparent in a study of living patients.

In conclusion, it appears that knowledge of a hypertensive patient's diabetic status, as revealed by the oral glucose-tolerance test, is at least as important as determination of blood-pressure in the assessment of possible risk of future coronary thrombosis, as judged on retrospective data.

If impaired glucose tolerance predisposes to cardiac infarction it seems possible that the mediating factor may lie partly in the alteration of blood coagulability in diabetes—support for this comes from the observations of Moolten *et al.* (1963) who showed that under certain conditions diabetics with coronary artery disease had abnormally enhanced platelet adhesiveness—or in reduced fibrinolytic activity (Fearnley *et al.* 1963), or in a combination of several such factors.

Summary

One hundred and seven patients, 46 males and 61 females, who were attending for treatment of hypertension were assessed from the standpoint of the presence or absence of evidence of coronary artery disease. An oral glucose-tolerance test was carried out on each patient. It was found that of all patients in the study group with evidence of coronary artery disease there were 35% with abnormal glucose tolerance whereas in those patients with no symptoms of coronary disease there were only 16% with abnormal tests. A higher percentage of patients with abnormal glucose tolerance was also noted in those in whom the only evidence of ischaemic heart disease was ST-segment depression in the electrocardiogram after exercise. The basal blood-pressure was not significantly different between those patients with and those without evidence of ischaemic heart disease.

The helpful criticism and encouragement of Sir Horace Smirk in the preparation of this paper are gratefully acknowledged. My thanks are also due to the Biochemistry Department of the Otago Medical School for carrying out the biochemical investigation, and to colleagues for referring patients for investigation; also to Mr. G. F. Spears for statistical assistance.

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Phenindione Sensitivity

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Brit. med. J., 1964, **2**, 730–732

Sensitivity reactions to phenindione began to be reported soon after its initial trials in the U.S.A., Canada, and Great Britain, and as early as 1954 Brown and MacMillan, from Toronto, decided to discontinue the use of the drug. They had carried out a randomized trial of four different anticoagulants, and two of the 261 patients treated with phenindione developed agranulocytosis, one case being fatal. Tait (1960) thought it "desirable to use alternative preparations," and Perkins (1962) pointed out that six deaths had been attributed to phenindione sensitivity. The *British Medical Journal* (1963) contrasted the lack of major toxic effects from the coumarins with the severe reactions sometimes caused by phenindione. There are now 34 papers with reports of severe sensitivity reactions to phenindione, and their authors are listed in the Bibliography. Many of the reactions have been multiple and include fever, rashes (both scarlatiniform and maculo-papular and often intensely pruritic), exfoliative dermatitis, eosinophilia, agranulocytosis, lymphadenopathy, stomatitis, pharyngitis, diarrhoea, steatorrhea, jaundice, and renal damage. This is excluding reports of lone skin rashes even though they may have forced a change to another anticoagulant, as occurred in 2% of Stafford's (1961) series.

We now report a further two cases in which sensitivity reactions have been associated with the use of phenindione. One had renal damage and one severe stomatitis, and in both a second course of the drug led to a return of the symptoms.

Case Reports

Case 1.—A 44-year-old tailor had an acute myocardial infarction for which he was treated with phenindione and from which he made a good recovery. Urine examination on admission to and discharge from University College Hospital revealed no abnormality. A maintenance dose of 100 mg. of phenindione daily was given and nine weeks after starting treatment oedema of the ankles and a purpuric rash over the legs developed and led to his admission to another hospital. Phenindione was stopped and the oedema and rash subsided. On discharge phenindione was restarted and a rapid return of the symptoms a week later led to his readmission to University College Hospital. Examination showed a fine purpuric rash on the legs and tender swollen ankles. The urine contained 10 g. of protein per litre and microscopy revealed numerous granular and cellular casts and very numerous pus cells. It was sterile on culture. Electrophoresis of the urinary protein revealed a typical glomerular proteinuria with a vast preponderance of albumin. Blood count, blood urea, and excretion pyelogram were all normal. Renal biopsy was attempted, but no kidney tissue was obtained. The oedema and purpura subsided rapidly when phenindione was stopped, but three months later moderate proteinuria was still present. Skin-testing was done by injecting 0.1 ml. of serum from patients taking phenindione, warfarin, and no drug, but no local reactions occurred.

Case 2.—A 38-year-old cashier was admitted to University College Hospital with an acute pulmonary embolus. He was treated with phenindione and was discharged taking 125 mg. daily. Thirty-one days after starting treatment he developed ulcers on the mouth, tongue, and gums which gradually worsened until phenindione was stopped on the 59th day of therapy. Three weeks later phenindione was restarted following the development of a leg-vein thrombosis, and the stomal ulcers recurred three days later. They again subsided when phenindione was withdrawn.

Discussion

Renal Damage by Drugs

A variety of drugs have been known to give rise to acute renal failure or to the nephrotic syndrome. The mechanism of the damage is thought to be a direct nephrotoxic effect with some drugs and a hypersensitivity reaction with others, though it is doubtful whether such a clear-cut differentiation can always be maintained. Direct renal damage occurs, for example, with mercury, gold, and potassium chlorate, while, among

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