BLOOD FIBRINOLYTIC ACTIVITY IN DIABETES MELLITUS AND ITS BEARING ON ISCHAEMIC HEART DISEASE AND OBESITY

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The clinical approach to occlusive vascular disease has been so dominated by coagulation on the one hand and by lipid metabolism on the other that many clinicians are unfamiliar with an enzymatic system in blood whose function seems to be the removal of deposited fibrin. Freshly obtained blood has spontaneous fibrinolytic activity—that is, the capacity to dissolve fibrin (Fearnley and Tweed, 1963 ; Fearnley and Lackner, 1955 ; Fearnley and Ferguson, 1958) ; and attention has been drawn to its probable role in maintaining vascular patency (Fearnley, 1953, 1960, 1961).

An apparent link between fibrinolysis and carbohydrate metabolism has been revealed by the response of blood fibrinolytic activity in diabetics to insulin (Fearnley, Vincent, and Chakrabarti, 1959) and in non-diabetic atherosclerotic patients to the sulphonylurea drugs (Fearnley, Chakrabarti, and Vincent, 1960 ; Tsapogas, Cotton, Flute, and Murray, 1962). Complementary perhaps is the abnormal carbohydrate metabolism found by Wahlberg (1962) in atherosclerotic patients free from clinical diabetes mellitus. For these reasons, and because of the well-recognized tendency of diabetics to ischaemic disease, we have studied blood fibrinolytic activity in 100 diabetic patients and in 100 age-matched controls free from diabetes and from detectable complications of atherosclerosis. The incidence of myocardial ischaemia in the diabetics has been classified in relation to their fibrinolytic activity.

Material and Methods

Diabetic Patients.—Studies were made of 100 diabetic out-patients (50 male, 50 female) aged 40–70 attending the diabetic clinics of the Gloucestershire Royal and Cheltenham General Hospitals. The only criteria, other than age limit, applied to the diabetic patients were that they should not be hypertensive or in ketosis. The upper limit of permitted diastolic pressure was 100 mm. Hg.

Control Patients.—These were selected from medical, surgical, and orthopaedic out-patients, excluding those with ischaemic, inflammatory, or neoplastic disease. The same upper limit of permitted diastolic pressure was applied. So far as possible we chose patients with trivial orthopaedic lesions and surgical conditions of a minor kind. Some patients with *x*-ray negative dyspepsia were included, but we avoided patients with evident psychoneurosis. The controls were age-matched with the diabetics as closely as possible in quinquennia.

Investigations.—A single blood sample was obtained from each patient between 11 a.m. and 12 noon. Blood glucose, serum cholesterol, and blood fibrinolytic activity were measured in the diabetics and the blood fibrinolytic activity alone in the controls. Every patient was weighed and measured and an obesity ratio $\frac{\text{weight in pounds}}{\text{height in inches}}$ was calculated.

Electrocardiography.—Both diabetics and controls had a 10-lead electrocardiogram (standard and unipolar limb leads, V1, V2, V4, V6). In the case of the controls any patient showing even minimal evidence of ischaemia or left ventricular hypertrophy was excluded from the series. The E.C.G.s of the diabetic patients were reported on blind—that is, without a knowledge of their lysis-times—by one of us (G. R. F.) ; doubtful changes were disregarded and only those considered to indicate myocardial ischaemia or the results of ischaemia were called positive. Flattening or inversion of the T waves in a number of leads, significant flat depression of the S-T segments, changes indicating past myocardial infarction, left ventricular hypertrophy, and left but not right bundle-branch block were accepted as evidence of ischaemic heart disease.

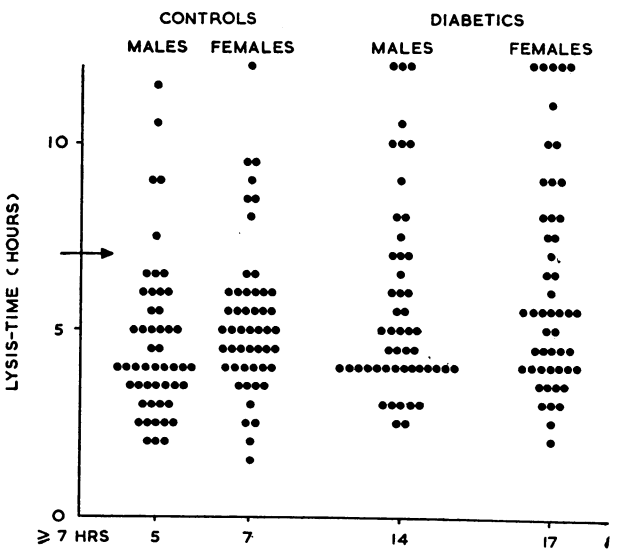
Blood fibrinolytic activity was estimated in duplicate by the method of Fearnley, Balmforth, and Fearnley (1957), with reading of the end-point modified as described by Fearnley and Chakrabarti (1962). The results were expressed as the mean of the duplicate determinations to the nearest half-hour. Fibrinolytic activity and lysis-time are reciprocal, so that a long lysis-time means low activity and a short lysis-time means high activity.

Results

The ages of the patients are shown in Table I. The lysis-times of all the diabetics and controls are shown in the Chart, and for ease of illustration all lysis-times

TABLE I.—*Age of 100 Diabetics and 100 Controls*

		40–44	45–49	50–54	55–59	60–64	65–69	Total
Male	Diabetic	6	8	8	10	9	9	50
	Control	6	10	10	8	8	8	50
Female	Diabetic	6	8	8	9	10	9	50
	Control	7	8	10	8	8	9	50



Lysis-time of 100 diabetic patients and 100 controls. In this figure all lysis-times greater than 12 hours are recorded as 12 hours. Fibrinolytic activity is arbitrarily defined as high when the lysis-time is <7 hours and as low when the time is ≥7.

greater than 12 hours are recorded as 12 hours. Table II gives the mean lysis-time of each group. It can be seen that the mean lysis-times of the diabetics (5 hr. 57 min.; 6 hr. 41 min.) were greater than those of the controls (4 hr. 32 min.; 5 hr. 9 min.) and that these differences are significantly greater than zero at the P=0.05 level for both sexes. The female controls and diabetics had longer mean lysis-times than their male counterparts, but these differences are not significant.

TABLE II.—*Mean Lysis-times of Controls and Diabetics*

	Male	Female	Both Sexes
Controls	4 hr. 32 min.	5 hr. 9 min.	4 hr. 50 min.
Diabetics	5 ,, 57 ,,	6 ,, 41 ,,	6 ,, 19 ,,
Difference	+1 ,, 25 ,,	+1 ,, 32 ,,	+1 ,, 29 ,,
Significant difference (P=0·05)	1·20	1·20	0·57

Fast and Slow Lysis-times.—By adopting a division of seven hours the diabetics and controls could be classified as showing rapid lysis (less than seven hours) and slow lysis (seven hours or longer). When the data were examined in this way (Table III) it was found that whereas only 10% of the male and 14% of the female controls had lysis-times of seven hours or longer the figures for the diabetics were 28% and 34% respectively. These percentages are significantly different at the P=0.05 level for both males and females.

TABLE III.—*Numbers of Diabetics and Controls with Long and Short Lysis-times*

Lysis-time	Males		Females	
	Control	Diabetic	Control	Diabetic
<7 hours	45 (90%)	36 (72%)	43 (86%)	33 (66%)
≥7 ,,	5 (10%)	14 (28%)	7 (14%)	17 (34%)
	(χ^2 (corrected) = 4·16 (P=0·04 approx.)		χ^2 (corrected) = 4·44 (P=0·03 approx.)	

Electrocardiographic Changes in Diabetics. — The incidence of electrocardiographic evidence of ischaemia in the diabetics in relation to lysis-times of less than seven hours and seven hours or longer is shown in Table IV. Fourteen of the male and 11 of the female diabetic patients had E.C.G. evidence of ischaemia. Although the incidence of ischaemic disease for each sex was approximately twice as great in those whose lysis-times were long as in those whose times were short, the differences are not statistically significant in the sexes

TABLE IV.—*Relation of Lysis-time to Ischaemic Heart Disease in Diabetics*

Lysis-time	No. of Patients	No. with Positive E.C.G.	Approximate Probability
Males ≥7 hours	14	6 (42·9%)	0·26
Males <7 ,,	36	8 (22·2%)	
Females ≥7 ,,	17	6 (35·3%)	0·21
Females <7 ,,	33	5 (15·2%)	
Combined ≥7 ,,	31	12 (38·7%)	0·06
Combined <7 ,,	69	13 (18·8%)	

separately. By combining the data for males and females the approximate probability is 0.06, which is sufficiently near the conventional level of significance of 0.05 to indicate the possibility of a real difference.

Obesity Ratio and Lysis-time.—The data showed an inverse relation between fibrinolytic activity and obesity. There was a significant relationship between the obesity ratios and lysis-times at the P=0.05 level in every group of patients except the female controls, and among the male controls this was highly significant (P=0.001).

Effect of Treatment.—Although the differences were not significant the mean lysis-times of the patients receiving insulin were shorter than those treated by diet alone or diet plus a sulphonylurea drug.

Age, Duration of Disease, Blood Sugar, Cholesterol.—There was no association between lysis-time and age in either diabetics or controls; and among the diabetics no correlation between lysis-time and duration of disease, blood-sugar level, or cholesterol level was found.

Discussion

Although for various reasons a single determination in out-patients has limitations as a test of the individual's fibrinolytic status—repeated estimations in the fasting, resting state in our experience being more reliable—nevertheless the results of this investigation indicate that diabetics as a group have lower fibrinolytic activity than healthy controls. The arbitrary division of fibrinolytic activity in terms of rapid lysis (<7 hours) and slow lysis (≥7 hours) makes this clear, since the incidence of slow lysis among the diabetics was twice to thrice that among their controls. The data relating low fibrinolytic activity and myocardial ischaemia, while insufficient statistically, accord with our observations in non-diabetic atherosclerotic patients, of whom rather more than 50% have low fibrinolytic activity when studied in the fasting, resting state. Others have investigated fibrinolytic activity in sufferers from present or past thrombotic episodes (Hume, 1958; Nestel, 1959; Lackner and Merskey, 1960; James *et al.*, 1961; Ogston, 1962), and the results, though varied, favour an association between defective fibrinolysis and ischaemic disease.

A correlation was found between low fibrinolytic activity and obesity, and this confirms Goldrick's (1961) observation, using the same method of measuring fibrinolysis as ourselves, on male white Australians. It was especially significant among the male controls (P=0.001 level) and insignificant among the female controls. If spontaneous fibrinolysis is one of the body's mechanisms for maintaining vascular patency it may be conjectured that this is consonant with the shortened life expectancy of the obese and the relative immunity of the female to arterial occlusion.

The somewhat shorter lysis-times of patients receiving insulin may have been due to the rebound increase of fibrinolytic activity found four hours after the injection (Fearnley *et al.*, 1959). The absence of correlation between cholesterol level and fibrinolytic activity accords with our findings in non-diabetic atherosclerotic patients.

Our data do not confirm the finding of Swan (1961) that blood fibrinolytic activity increases with age; his lysis-times were measured, however, with 50% plasma clots, and his subjects were males whose ages ranged from 21 to 87—a wider range than that of our patients.

These observations are not solely of academic interest, since the possibility exists of increasing blood fibrinolytic activity pharmacologically. Our further experience of the sulphonylureas given to atherosclerotic patients for this purpose has been disappointing because many develop resistance, but testosterone and nandrolone have proved more reliable (Fearnley and Chakrabarti, 1962), and recently we have found a moderate dose of phenformin to be equally promising. A sustained increase of blood fibrinolytic activity by oral medication would

enable the relevance of spontaneous fibrinolysis to the problem of occlusive vascular disease to be tested by long-term therapeutic trial.

Summary

Blood fibrinolytic activity was compared by a single estimation in 50 male and 50 female diabetic out-patients, and in equal numbers of age-matched controls selected because of freedom from occlusive vascular disease. The diabetics as a group had lower fibrinolytic activity than the controls, and among the diabetics electrocardiographic evidence of myocardial ischaemia occurred twice as commonly in those whose fibrinolytic activity was low as in those whose fibrinolytic activity was high.

A significant inverse relationship between obesity and fibrinolytic activity was found in every group of patients except the female controls. There was no association between age and fibrinolytic activity, and among the diabetics no correlation between fibrinolytic activity and duration of diabetes, blood-sugar level, or cholesterol level.

These observations suggest that spontaneous fibrinolysis is of importance. If the function of fibrinolysis is to maintain vascular patency the possibility of enhancing its action pharmacologically may permit a fresh approach to the problem of occlusive vascular disease.

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Uganda has become a full member of the World Health Organization. This brings the total number of W.H.O. members up to 117, of which one, Rhodesia and Nyasaland, is an associate. Jamaica, formerly an associate member, is now eligible for full membership since it has attained its independence: and the United Kingdom has indicated its intention of seeking associate membership for Mauritius, for whose foreign relations it is responsible.

CATHETER-INDUCED URINARY INFECTION: FOLLOW-UP STUDY

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The passage of a catheter has been shown to cause urinary infections in a proportion of female patients, and it has been held that such infections may initiate chronic and progressive renal damage. However, to our knowledge, no prospective study has so far been published which establishes the frequency with which this occurs. In an attempt to study this we have re-examined as many as possible of the 102 patients described by Durham *et al.* (1954). Of these patients, who had undergone operations for vaginal repair in 1953, 90 developed urinary infections which were ascribed to catheterization. Eighty-two of these infected patients received treatment and 73 had sterile urine at a single examination before discharge, in some cases while the drug was still being given or immediately after the end of a course. Thus in 17 patients infection was still present on discharge. It is possible that the 73 patients with sterile urine were, in fact, cured, but it is unlikely. Other work—for example, that of Garrod *et al.* (1954)—suggests that re-examination a month or so later would have shown some of these patients again to have urinary infections.

Materials and Methods

Letters were written in 1961 and 1962 to all patients believed to be alive and likely to be able to attend hospital; in the remaining cases the general practitioners were consulted. For those known to have died, reference was made to various sources, including the General Register Office. All patients who attended hospital were examined by a physician and a gynaecologist. Mid-stream specimens of urine were collected for bacteriological examination and were examined by a quantitative plate method (Cattell and Lefford, 1963). Blood urea and serum creatinine values were also determined.

Results

Seventy-one patients were seen, 17 were reported on by their own doctor, and 10 were known to be dead. The Table shows these patients, their age in 1953, and what little is known of the remaining four patients.

Age Distribution

1961–2	Age in 1953						
	Total	25–	35–	45–	55–	65–	75–
Patients seen	71	4	14	27	22	4	0
,, reported on by G.P.	17	0	2	3	6	6	0
Patients known to be dead	10	0	1	2	5	1	1
Miscellaneous*	4	0	1	1	1	1	0

* Two patients known to be alive (one in good health, one under care of a homoeopath) and two patients untraced (one thought to have emigrated, one thought to be dead).