Summary

The increasing recognition of non-arteriosclerotic endomyocardial fibrosis as a significant cause of congestive cardiac failure in adults outside Africa as well as in Africa is noted. Five new cases occurring in Great Britain (one in an African) are added to the mounting literature on the subject. The main clinical and pathological features are summarized, and the suggestion is made that early consideration of the diagnosis may permit some control of the complications of the disease and effect an improvement in the prognosis.

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Fibrinolytic Activity and Thyroid Function

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Hypothyroidism is a condition which is associated with atherosclerotic changes in arteries, especially the coronary, renal, and cerebral arteries (Fishberg, 1924 ; Douglass and Jacobson, 1957). In spite of this, however, the reported incidence of angina of effort in untreated hypothyroidism is small. Willius and Haines (1925) found only one case out of 162 patients studied, and Smyth (1938) found two cases out of 108 patients. On the other hand, on giving thyroid to such patients the incidence of angina increases to 16% (Wayne, 1960). Not only is angina unusual, myocardial infarction also seems to be an uncommon event in the untreated case. There is, however, no information in the literature on this aspect of hypothyroidism. During the years 1952 to 1962 3,026 patients with myocardial infarction were admitted to the Southern General Hospital, Glasgow. Of these, 58 were receiving thyroid for hypothyroidism but none had untreated hypothyroidism.

Smyth (1938), after reviewing the literature, concluded that the number of reported cases of death from myocardial insufficiency in patients with untreated hypothyroidism is remarkably small. Nevertheless, it is well recognized that the overenthusiastic administration of thyroid to such patients carries a risk of precipitating a myocardial infarction (Salter, 1941 ; Wallach *et al.*, 1958 ; Wayne, 1960). It is claimed that the infarction occurs in the absence of a coronary artery thrombus (Wood, 1956). The event is explained on the basis of ischaemic necrosis resulting from the increased metabolic demand of the myocardium as a consequence of thyroid administration and the inability of atheromatous coronary arteries to effect an increased blood supply to the myocardium. However, of nine reported deaths attributed to thyroid administration to previously untreated patients with hypothyroidism and on whom necropsies were performed, four were found to have a demonstrable thrombus in a coronary artery (Willius and Haines, 1925 ; Fahr, 1932 ; Smyth, 1938 ; La Due, 1943 ; Wallach *et al.*, 1958). This is approximately the same proportion of thrombi demonstrable at necropsy in uncomplicated myocardial infarction (Branwood and Montgomery, 1956).

Since it appears as though the hypothyroid patient is in some way spared from the effects of the accompanying arterial disease until thyroid is administered, and as vascular disease (Sawyer *et al.*, 1960), in particular acute myocardial infarction (Hume, 1958), has been reported to be associated with reduced fibrinolytic activity, it seemed important to determine whether alterations in thyroid function were associated with changes in fibrinolytic activity.

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Material and Methods

Patients (see Table).—These consisted of 75 female subjects who had been referred to the thyroid clinic at the Western Infirmary for diagnostic radioactive-iodine studies. They were seen on a Monday between 8.45 and 9.15 a.m. prior to the administration of a tracer dose of radioactive iodine for diagnostic purposes. The subjects had had only tea and toast for breakfast. All were out-patients. Blood was withdrawn from an antecubital vein and 9 ml. delivered into a warmed graduated centrifuge tube containing 1 ml. of 3.8% sodium citrate. This blood was used for the measurement of fibrinolytic activity, fibrinogen, and cholesterol levels. At the end of the experiment the patients were divided into the following groups on the basis of age and the results of the conventional radioactive-iodine studies. Eight patients were excluded because of equivocal radioiodine results.

Results Expressed as the Means with One Standard Deviation. Fibrinolytic Activity Also Expressed as a Median Because the Distribution Curve was Skewed

Group	No. of Patients	Age (Years)	Fibrinogen (mg./100 ml.)	Fibrinolysis %		Cholesterol (mg./100 ml.)
				Median	Mean	
Ia	21	38·7 ± 6·2	238·2 ± 51·5	15·3	15·3 ± 4·9	173·5 ± 26·8
Ib	18	59·3 ± 5·7	317·2 ± 86·4	15·5	22·8 ± 19·2	205·9 ± 41·1
IIa	13	36·7 ± 6·8	283·3 ± 64·2	10·6	17·6 ± 18·2	129·7 ± 23·4
IIb	7	56·1 ± 5·0	275·1 ± 56·1	12·9	26·0 ± 29·9	129·8 ± 16·1
III	16	56·8 ± 7·4	291·0 ± 50·9	62·5	55·9 ± 33·7	261·0 ± 64·1

Group Ia, 21 euthyroid patients under the age of 50.

Group Ib, 18 euthyroid patients aged 50 and over.

Group IIa, 13 hyperthyroid patients under the age of 50.

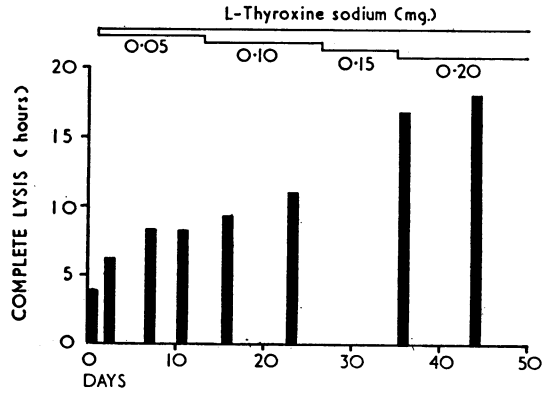
Group IIb, 7 hyperthyroid patients aged 50 and over.

Group III, 16 hypothyroid patients aged 50 and over.

Fibrinogen was prepared by the phosphate-buffer method of Jacques (Biggs and Macfarlane, 1957). Radioiodinated

fibrinogen was prepared by the method of Clement and McNicol (1959). Radioactive plasma: to 10 ml. of expired blood-bank plasma was added 0.1 ml. of radioactive fibrinogen and stored at −20° C. until required for use. Thrombin (Maws) solution was diluted to 10 units/0.1 ml. and stored at −20° C. Serum fibrinogen was measured by the micro-Kjeldahl apparatus. Serum cholesterol was measured by the method of Abell *et al.* (1958).

Fibrinolytic Activity.—2 ml. of citrated whole blood, immediately after withdrawal, was placed into a 6 by ½ in. (15 by 1.3 cm.) test-tube warmed to 37° C. in an incubator. The test-tube contained 0.1 ml. of radioactive plasma. 10 units of thrombin was then added and the mixture was stirred briskly with an orange stick, the clot being allowed to form round the stick. Incubation at 37° C. was continued for 24 hours. After the incubation the orange stick was removed with the residual adherent clot and placed in another 6 by ½ in. (15 by 1.3 cm.) test-tube. The clot was then washed with 2 ml. of normal saline and the washing placed in a third and similar test-tube. The radioactivity of the three tubes was measured by placing the tubes in a well scintillation counter. The sum of radioactivity of the three tubes minus the radioactivity remaining in the residual clot was expressed as a percentage of the total radioactivity of the three tubes: that is, the more fibrinolysis the less radioactivity remaining in the clot and the greater the percentage lysis. Duplicate observations on four patients showed the method to be reproducible. Serial observations were also made on one case of severe hypothyroidism to determine the effect of thyroxine therapy. The complete lysis time of the citrated whole blood clot was used as a measure of fibrinolytic activity (see Chart).



Complete lysis (hours) is the time taken for a whole citrated blood clot to be completely digested.

Statistics.—Two sets of means were compared by t-tests, except in the case of the fibrinolytic activity, where Wilcoxon's test was used because the distribution curve was skewed. The median fibrinolytic activity is used for purposes of comparison.

The Table on page 686 gives the findings from the following investigations.

Results

Ages.—There was no significant difference between the mean ages of the groups below 50 or between the mean ages of the groups over 50.

Fibrinolysis.—The median fibrinolytic activity of group III was significantly higher than the median fibrinolytic activity of all the other groups ($P<0.001$). There was no significant difference between groups IIa and IIb or between groups Ia and Ib. There was no significant difference between all the euthyroid subjects taken together, although there was a trend from thyrotoxic to euthyroid to hypothyroid state.

Fibrinogen.—Group Ia had significantly less fibrinogen than the older euthyroid group Ib ($P<0.01$). There was no significant difference between groups IIa and IIb, but group IIa had significantly more fibrinogen than group Ia ($P<0.05$). Group III did not differ from groups IIa and IIb or from group Ib, but was significantly greater than group Ia ($P<0.01$).

Cholesterol.—The mean cholesterol level of group III was significantly higher than the mean cholesterol level of group Ib ($P<0.01$) and both groups Ia and Ib had significantly more cholesterol than groups IIa and IIb ($P<0.001$). Group Ia had significantly less cholesterol than group Ib ($P<0.01$), but there was no difference between groups IIa and IIb.

Discussion

Analysis of the results reveals that untreated hypothyroid patients have significantly more fibrinolytic activity than either euthyroid or thyrotoxic subjects ($P<0.001$). There is a trend for the fibrinolytic activity to increase from thyrotoxic state through euthyroid to hypothyroid state, but this was not statistically significant. It seems possible that this increase in fibrinolytic activity provides a protective mechanism by which the untreated hypothyroid patient is spared the consequences of occlusive vascular disease and that the introduction of thyroid therapy upsets the balance of activators and inhibitors of the fibrinolytic system in favour of thrombus formation. This contention is supported by the observation that thyroxine appears to have depressed the fibrinolytic activity of the patient illustrated in the Chart. Furthermore, it would be interesting to determine whether increased fibrinolytic activity is a factor involved in the haemorrhagic phenomena which sometimes complicate hypothyroid coma (Orr, 1962).

The observation that fibrinogen increases in females after the menopause (Hume, 1961) was also confirmed in the present study in the euthyroid group. It was found, however, that thyrotoxicosis abolished this effect by increasing significantly the level of fibrinogen in the younger women. This probably reflects an increased production of fibrinogen. Similarly an increase in cholesterol level in post-menopausal women is also confirmed (Lund *et al.*, 1961) and is abolished by the onset of thyrotoxicosis, which lowers the cholesterol levels in both young and old thyrotoxics to the same level and below that of the euthyroid groups. The hypothyroid patients had significantly more cholesterol than the other groups, but the cholesterol levels did not correlate individually with the fibrinolytic activity, nor did the fibrinolytic activity in the hypothyroid group correlate with the thyroid-gland uptake of radioiodine or the blood radioactive protein-bound iodine.

Summary

Euthyroid, thyrotoxic, and hypothyroid subjects have been examined with regard to fibrinolytic activity and cholesterol and fibrinogen levels in the blood. Cognizance was taken of age. All were female subjects. It was found that hypothyroid subjects had significantly more fibrinolytic activity than the other two groups. Observations in one case of hypothyroidism revealed that thyroid administration could depress the fibrinolytic activity. It is suggested that this may be an important factor in the production of myocardial infarction following thyroid administration to hypothyroid subjects. That fibrinogen increases with age was also confirmed, but it was found that young women with thyrotoxicosis had fibrinogen levels significantly higher than the young euthyroid group, suggesting an increased production of fibrinogen in this group. No unexpected findings were noted in the cholesterol measurements.

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Reduced Platelet Survival in Patients with Starr–Edwards Prostheses*

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It is well recognized that patients with valvular disease of the heart are particularly susceptible to the complications of thrombosis and embolism, especially if the mitral orifice is stenosed. In recent years valvular repair by a variety of prosthetic procedures allowed the hope that such complications might be avoided. Unfortunately, thrombosis and embolism have continued to occur, often at a long interval after successful operations of this type. The finding of thrombi attached or in close proximity to artificial prostheses has led to the continued modification of such prostheses and operative techniques and to the extensive use of long-term anticoagulant therapy post-operatively (*Lancet*, 1962).

As many such thrombi have been composed mainly of platelets and fibrin, we have investigated the behaviour and survival of radiochromate-labelled platelets in patients who have undergone successful valve replacement with Starr-Edwards ball-valve prostheses (Starr and Edwards, 1961; Starr *et al.*, 1962).

Subjects Studied and Methods

Eight studies have been carried out in seven subjects. Two were males and five females. Their ages ranged from 24 to 64 years. In each instance the operation was performed by Mr. H. D'Arcy Sutherland with the assistance of members of the Cardiac Surgery Unit of the Royal Adelaide Hospital. In five subjects the mitral valve had been replaced and in two the aortic. All had been considerably improved by operation, and none was in cardiac failure. One subject (R. J.) was studied twice. Details relating to each subject are included in the Table.

Platelets from each subject were labelled with 70–100 microcuries of radiochromate *in vitro* and reinfused into the donor, in whom their behaviour, survival, and distribution in the body were studied.

Details of the procedure employed have been described previously (Davey and Lander, 1963), except that the blood from which the platelets were separated was collected in the more acid solution of acid-citrate-dextrose (A.C.D. "S") suggested by Aster and Jandl (1964), instead of in a solution of ethylenediaminetetra-acetic acid (E.D.T.A.).

Platelet radioactivity was measured in samples of blood collected at frequent intervals for four hours following infusion of the labelled platelets and at daily intervals for at least 10 days. In addition, activity over the heart, lungs, liver, spleen, and sacrum was determined daily by external scintillation counting (Lander and Davey, 1964a). Platelet counts were performed on all samples of blood by the method of Brecher and Cronkite (1950).

Results

In all subjects infusion of the labelled platelets was followed by the normal phenomenon of transient "segregation" and subsequent re-entry into circulation of a proportion of the labelled platelets (Davey and Lander, 1964). However, as found by Aster and Jandl (1964), the degree of segregation is less when A.C.D. "S" is used as anticoagulant than when E.D.T.A. is used.

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Data Relating to Patients Studied

Subject	Sex	Age	Valve Replaced	Time After Operation (Weeks)	Anticoagulant	Thrombosis or Embolism	Platelet Count (per c.mm.) Mean and Range	Platelet Survival
J.K.	F	49	Mitral	25	Phenindione		313,000 (207,000–369,000)	Normal
E.K.	F	59	Mitral	29	Phenindione	Cerebral; pre-operative and early post-operative	232,000 (183,000–345,000)	Normal
S.R.	F	24	Mitral	32	Phenindione		240,000 (180,000–327,000)	Norma
R.J.	M	64	Aortic	45	Nil	Cerebral; post-operative*	230,000 (168,000–294,000)	Normal
				48	Phenindione		251,000 (207,000–324,000)	Normal
S.M.	F	51	Aortic	46	Nil		214,000 (180,000–273,000)	Reduced
R.L.	M	37	Mitral	46	Phenindione	Cerebral; pre-operative	254,000 (207,000–360,000)	Reduced
P.B.	F	52	Mitral	52	Phenindione		244,000 (180,000–360,000)	Reduced

* See text.