Original copy.

J. D. CASH.

Leslie (William) Prize in Medicine (1966)

The effect of exercise and adrenaline stimulation of the fibrinolytic enzyme system in young men and women.

J. D. CASH. B.Sc., M.B., Ch.B.

INTRODUCTION

More than a hundred years ago, Rokitansky (1842) postulated that fibrin deposition on the arterial wall was the cause of atherosclerosis. Duguid (1948, 1949, 1955) subsequently produced histological evidence supporting this hypothesis by observing fibrin deposition on the arterial intima, followed by endothelial covering and final incorporation into the vessel wall. This work has been partially confirmed by Harrison (1948), Hend (1949), Crawford and Levene (1952) and Ambrus et al. (1958).

In 1908, Nolf suggested that fibrin deposition (coagulation) and removal (fibrinolysis) might be in a state of dynamic balance. This hypothesis has been supported by the work of Copley (1954, 1957), Roos (1958), Fearnley (1961)and Salmon (1961) and was extended by Astrup (1956) who envisaged a continuous and balanced deposition and lysis of fibrin. Astrup further postulated that shifting of this equilibrium, so producing disequilibrium, would result in bleeding on the one hand or atherosclerosis and/or thrombosis on the other.

The evidence that defective fibrinolysis is associated with occlusive vascular disease remains controversial. In a recent review of the present information, Fearnley (1965) has concluded that there is little evidence of a difference in blood fibrinolytic activity between males with overt coronary artery disease and aged matched controls. However, there is some reason to believe that defective fibrinolysis is present in post-menopausal women, in women with ischaemic heart disease and in both sexes suffering from peripheral atherosclerosis.

It is possible that much of the present uncertainty arises from the known fact that blood fibrinolytic activity fluctuates, in any one person, from day to day and throughout the same day (Fearnley 1959, and Blix 1961). Thus unless an extreme difference exists between patients suffering from atherosclerosis and controls, comparison by single estimations might fail to yield satisfactory information.

In the light of Astrup's hypothesis, it is unlikely, on theoretical grounds, that disequilibrium would be more than a transitory phenomenon, without death rapidly supervening. It is possible that there is little difference in blood fibrinolytic activity between these two groups, in the resting state. The logical extension of this concept would be that disequilibrium does not usually occur in the resting state but may arise, transiently, during physiological episodes which are known to stimulate an increase in both coagulation and fibrinolysis. It is postulated, therefore, that a defective fibrinolytic system might be more readily demonstrated in certain individuals, by observing their fibrinolytic response to stimuli known to increase both coagulation and fibrinolysis. If such a group were isolated, then it is suggested that these persons would be more liable to episodes of coagulation - fibrinolysis disquilibrium.

EXPERIMENTAL DESIGN

There is considerable evidence to show that exercise (Biggs et al. 1947,

Truelove 1951, Fearnley and Lackner 1955, Sherry et al. 1959, Billimoria et al. 1959, Ogston and Fullerton 1961, Iatridia and Ferguson, Jange et al. 1964, Ogston and McAndrew 1964 and Burt et al. 1964) and parenteral adrenaline (Macfarlane and Biggs 1948, Truelove 1951, Genton et al. 1961, Doni et al. 1963, Tanser and Smellie 1964) increase plasma fibrinolysis, and that this is due to a release of plasminogen activator. Careful analysis of the results of these workers reveals that some of their subjects responded poorly. Those who have commented on these poor responders have given tentative explanations. Biggs et al. (1947) thought increased physical fitness relevant, Sawyer et al. (1960) inappropriate timing of sample collection, whereas Iatridis and Ferguson (1963), suggested that the reason might be the failure to show the usual reaction to stress or to the production of a fibrinolytic inhibitor. It is not possible to make any valid conclusions from these studies, however, because of the variation in fibrinolytic assays and in the type of exercise used in different laboratories. Of no less importance is the fact that in most studies exercise to exhaustion was used and therefore no attempt was made to examine individual reproducibility of response.

The subsequent sections describe the results of series of experiments, on a group of young healthy human volunteers, aged 18–30 years, whose fibrinolytic systems were stimulated by a standard exercise procedure and intravenous adrenaline. Each experiment was performed at weekly intervals for all subjects.

MATERIALS

Anticoagulant

Sodium Citrate B.P. 3.8%.

Buffers

(a) Barbiturate Buffer Modified veronal buffer of pH 7.4 and ionic strength 0.15 (Owren 1947).

(b) Tris Buffer A 0.15M solution of tris - (hydroxymethyl) - amino methane. (Koch-Light Laboratories Ltd. Batch No. 11342) adjusted to pH 7.8.

(c) Phosphate Buffer 0.1M at pH 7.6.

Fibrinogen

A Blömback and Blömback (1956) preparation of human fibrinogen with a clottability of 97% (Supplied by Kabi Pharmaceutical Company. Batch No. 83164) was used. A 1.5G% solution of fibrinogen in tris buffer was stored in plastic tubes at -20°C. After thawing it was diluted to 0.15G% in tris buffer and used for fibrin plates.

Thrombin

Topical thrombin (Parke Davis and Co. Batch No. 031798A) was used. A solution of 500 u/ml. in tris buffer was prepared for fibrin plates, one of 50 u/ml. in barbiturate buffer for euglobulin lysis time estimation and one of 1000 u/ml. in physiological saline for fibrinogen estimations. All these solutions were stored at -20°C in plastic tubes and used immediately after

thawing.

Streptokinase

The preparation produced by Lederle Laboratories (Batch No. 2201-66) was used for plasminogen assays. It was diluted to 2000 u/ml. in phosphate buffer and stored in plastic tubes at -20°C.

Urokinase

The Standard Reference preparation (2400 Plough units) produced by Leo Pharmaceuticals, Denmark (Batch No. 63062) was used. Solutions of 3.0 u/ml. in tris buffer were prepared and stored at -20°C in plastic tubes.

Glassware

All glassware was siliconised using a 3% solution of I.C.I. M550 silicone in trichlorethylene.

METHODS

Exercise Procedure

All experiments were carried out during the morning, after a light breakfast in a procedure room at 19-20°C. Subjects abstained from smoking and excessive exercise on the morning prior to the experiment, and were required to rest, lying down, for 30 minutes before the initial venepuncture. At the end of the rest period each subject walked at 3.4 m.p.h. on a treadmill at 5° elevation for a period of 8 minutes. They were required to adjust their stride to 120 paces per minute. Pulse rates immediately before and

after the exercise were recorded on an electrocardiograph.

Adrenaline Infusions

Following the standard 30 minute rest period, a 21 gauage needle was inserted into a cubital vein, a blood sample withdrawn, the syringe detached and a connection to the pump made with the indwelling needle. A 2 minute infusion of adrenaline (10 microgram/1.95m^2 surface area/min) in 20 ml. of saline was started immediately using a Harvard Pump. At the end of the infusion the needle was withdrawn. 2 minutes after the end of the infusion a second blood sample was withdrawn from the cubital vein in the opposite arm.

Blood Sampling and Centrifugation

9 mls. of blood were withdrawn from a vein in the cubital fossa, by clean venepuncture, with the minimum of venous occlusion, into a siliconised syringe. The blood was immediately transferred to a previously cooled centrifuge tube, in melting ice, containing 1 ml. of 3.8% sodium citrate. The first sample remained in the melting ice until the second sample was withdrawn, immediately after the exercise (or 2 mins after the adrenaline infusion), and then both were centrifuged at 3,400 r.p.m. at +4^{o}C for 2 minutes in a refrigerated centrifuge. The upper third of the plasma was transferred, using a siliconised pasteur pipette, into a pre-cooled plastic tube: euglobulin precipitation was performed immediately.

Euglobulin Lysis Time

1 ml. of plasma was transferred to a siliconised centrifuge tube in melting ice, containing 19 mls. distilled water and 0.18 ml. 1% acetic acid.

The pH was finally adjusted to 6.0 on a Beckman Zeromatic pH meter, using 0.25% acetic acid. Precipitation time was 10 minutes from the addition of the plasma and was done in melting ice. The euglobulin suspensions were then centrifuged at 3,400 r.p.m. for 20 minutes at +4°C. The supernatant was discarded, the inside of the centrifuge tube wiped dry with a tissue and the precipitage resuspended in 1 ml. of barbiturate buffer pH 7.4. 0.24 ml. of this euglobulin solution was transferred, in triplicate to 3" x $\frac{3}{8}$" siliconised test-tubes and 0.24 ml. thrombin solution (50 u/ml. in barbiturate buffer pH 7.4) added immediately. The test-tubes were placed in a water-bath at 37°C and the time taken from the addition of thrombin to complete lysis was recorded as the euglobulin lysis time.

Inhibitor Assay

Inhibitor assays were based on the method of Blix (1964). Human fibrin plates were prepared by a modification of the method of Astrup and Mullertz (1952). 10 mls. of 0.15G% human fibrinogen in this buffer were pipetted into a plastic petri dish, internal diameter 8.8 cms. and, before clotting with 0.2 ml. thrombin solution (50 u/ml. in tris buffer) on a level table, 1 ml. of euglobulin solution diluted in saline was added and thoroughly mixed. A series of four plates were used containing dilutions of $\frac{1}{10}$, $\frac{1}{25}$, and $\frac{1}{50}$ and a control with 1 ml. saline. Thence, 0.03 ml. drops of Urokinase (3.0 u/ml. in tris buffer) were placed on to the fibrin film in triplicate 20 minutes after clotting. The plates were incubated at 37°C for 24 hours and the product of the perpendicular diameters taken as a measure of fibrinolytic activity.

Fibrinogen Assay

The method of Ratnoff and Menzie (1951), as modified by Alkjaersig (1960).

Plasminogen Assay

The caseinolytic assay of Remmert and Cohen (1949) as modified by Alkjaersig et al. (1959).

RESULTS

(a) Resting Levels of Euglobulin Lysis Time

Table 1 shows the results in detail of all experiments. The resting level of plasminogen activator, as measured by the euglobulin lysis time, varied from subject to subject and from day to day in the same subject. This variation could not be correlated with the euglobulin fibrinogen and plasminogen (Fig. 1). No urokinase inhibitor was demonstrated in the euglobulin solutions. The females had a lower euglobulin lysis time then the men, which was highly significant ($p < 0.001$).

Table 2 shows the results during a menstrual cycle in 9 female subjects. There were no significant changes related to the phases during the menstrual cycle.

(b) The Fibrinolytic Response to Moderate Exercise

If A and B represent the resting and post-exercise euglobulin lysis times, respectively, then the percentage increase following exercise was calculated as $\frac{A-B}{A} \times 100$. The results of this calculation are shown in Table 1 for each experiment, and also the mean percent response for each

individual. The results indicated that, for any one subject, the fibrinolytic response was reproducible (correlation coefficient (r) = 0.9929 and $p < 0.001$). Furthermore, there was a highly significant individual variation in response (analysis of variance showed F = 36.7 which was significant at the 1% level).

Fig. 2 shows the frequency distribution of the percent response in all the subjects and Fig. 3 demonstrates that the females produced a significantly greater fibrinolytic response than the males ($p < 0.001$). The individual variation in fibrinolytic response did not correlate with the pulse rate increase following exercise (Fig. 4 and Table 3). There was, however, a highly significant greater pulse response in the female subjects ($p < 0.001$).

There appeared to be no significant changes in the fibrinolytic response to moderate exercise throughout a menstrual cycle, in the 9 females studied (Table 2).

(c) Intravenous Adrenaline Studies

(1) Timing of maximum response

Fig. 5 shows the euglobulin lysis time in blood samples taken before, during and after the adrenaline infusions. It confirms the findings of Genton et al. (1961) that the maximum fibrinolytic response occurs 2 minutes after the end of the infusion.

(2) Fibrinolytic response to I.V. adrenaline

Table 4 represents the findings before and 2 minutes after the adrenaline infusion.

The percent response was calculated as for the exercise studies in 25

subjects. Individual reproducibility of fibrinolytic response was demonstrated ($r = 0.9959$ $p < 0.001$) and there was a significant difference between individuals ($F = 28.9$ which was significant at the 1% level). There was considerable variation in subjective responses: none were described as unpleasant. There was no apparant correlation between the subjective and fibrinolytic responses.

Fig. 6 shows the relationship between the fibrinolytic response to moderate exercise and intravenous adrenaline in 24 of the subjects. There appears to be a good correlation ($r = 0.855$ $p < 0.001$).

DISCUSSION

We have confirmed the findings of Blix (1961) that, even under carefully standardised assay procedures, the resting euglobulin lysis time varied from subject to subject and from day to day in the same subject. Despite the criticism of substrate variability, the euglobulin lysis time has been shown to be a good measure of plasminogen activator (Sawyer et al. 1960, Iatridis and Ferguson 1963, Fletcher et al. 1964). We were unable to attribute the daily fluctuations in the euglobulin lysis time to the changes in euglobulin fibrinogen and plasminogen, nor was there evidence of a urokinase inhibitor in those euglobulin fractions giving a long lysis time. Although this problem is under investigation in this laboratory, there is, as yet, insufficient evidence to exclude the possibility that the daily resting level of circulating plasminogen activator may indeed vary in any one individual.

Furthermore, it would appear, as suggested by Fearnley (1961), using the dilute blood clot assay technique, that this daily fluctuation is more pronounced in some individuals than others.

The finding of a significant sex difference in the resting euglobulin lysis time is contrary to the observations of Beller et al. (1964) and Brakman et al. (1966). There is no explanation for this apparent discrepancy, but it may be relevant that previous conclusions have been reached, in the main, from single observations. It has been confirmed, however, that the daily fluctuations in the resting euglobulin lysis time do not appear to be related to the menstrual cycle.

Despite this daily fluctuation, the level following a standard exercise procedure, in the same subject, appeared to be related in a constant way. Thus, the fibrinolytic response (which has been termed fibrinolytic reactivity) to a fixed moderate exercise procedure, expressed as a percentage of the pre-exercise level, in normal young subjects, is a reproducible phenomenon. There appears to be individual variation and there exists a small, but definite, group of poor responders. Of no less interest was the finding that women, of the same age group, seem to have a greater fibrinolytic reactivity than men, and that in the group studied, no female poor responders were discovered. There appeared to be no significant change in fibrinolytic reactivity during the menstrual cycle.

It is possible that the variation in fibrinolytic response may simply mirror the individual varation in stress to a standard exercise procedure.

If pulse rate response is a measure of the exercise stress, then the absence of a correlation, within each sex group, would not confirm this view. When the two sex groups are compared, however, the position is less clear. The females showed a significantly higher pulse response than the males. This finding is in agreement with the work of Åstrand (1952) who suggested that the cause might be a stronger distaste in women for physical exertion, or, that men may be more efficient working machines.

The significance of the fibrinolytic reactivity to exercise remains, as yet, unknown. There is evidence to show that adrenaline production increases during muscular work (Euler and Hellner 1952, Holmgren 1956) and that this increase shows some individual variation (Vendsalu 1959). Although this would be an acceptable explanation for the difference in fibrinolytic reactivity between the subjects in this study, the results of the adrenaline infusions studies, although limited, would not support this interpretation. It is postulated, therefore, that the fibrinolytic reactivity to exercise may represent, in part, the ability of an individual to generate circulating plasminogen activator to stress. The results of this study would suggest that in some individuals this ability is poor.

It is not possible to explain the group of poor responders on the basis of physical fitness (Biggs et al. 1947). Four of the volunteers were highly trained atheletes and their mean percent response ranged from 24 - 54%. Iatridis and Ferguson (1963) demonstrated the generation of a fibrinolytic inhibitor following exercise in one of their twelve poor responders.

No increase in urokinase inhibitor content of the post-exercise plasma was detected, nor in any euglobulin fraction precipitated at pH 6.0. Exercise also increases coagulation (Vurori 1950, Bond et al. 1961, Iatridis and Ferguson 1963, Burt et al. 1964, Von Kaulla and Von Kaulla 1964), yet, Iatridis and Ferguson observed 12 of their 59 young subjects, in which increased coagulation was demonstrated, failed to increase their circulating plasminogen activator. Burt et al. (1964) concluded that the mean change following strenuous exercise in 44 young subjects was in favour of fibrinolysis. Examination of their results in more detail shows that 2 subjects gave poor fibrinolytic responses associated with a normal increase in coagulation.

Mental stress also stimulates both coagulation and fibrinolysis (Macht 1952, Dreyfuss 1956, Friedman et al. 1958, Ogston et al. 1962). It is postulated, therefore, that the possibility arises that persons with a poor fibrinolytic reactivity may be subject to episodes of coagulation - fibrinolysis disequilibrium during their day to day living. In the light of Astrup's hypothesis these persons may be at risk to atherosclerosis and/or thrombosis.

Evidence supporting this view is fragmentary. Cirrhotic patients have a low incidence of myocardial infarction (Grant et al. 1959, Howell and Manion 1960), and it has been shown that they may possess an exaggerated fibrinolytic reactivity (Weiner 1963, Fletcher et al. 1964) as well as a general tendency to hypocoagulation (Ollendorff et al. 1966). Von Kaulla and Von Kaulla (1964) have provided suggestive evidence that patients, with a proven history of myocardial infarction, may show an exaggerated hypercoagulability following exercise.

There is reason to believe that atherosclerosis may be prevalent in young males (Thomas 1957, Holman et al. 1958) and that women, during the reproductive period of their lives, are relatively immune (Thomas 1957, Strong and McGill 1962). The finding of a small group of apparently normal young men with poor fibrinolytic reactivity to moderate exercise, and that women, of the same age group, have a greater fibrinolytic reactivity may prove, therefore, to be of some interest. It is suggested that the study of coagulation and fibrinolysis, simultaneously, before and following stimulation of these systems may prove to be a more relevant focussing point for observing potential states of coagulation - fibrinolysis disequilibrium than a measurement of these parameters in the resting state, as has been the practice in the past, (Hume 1958, Lackner and Merskey 1960, Nestel 1960, Ogston 1962, Katz et al. 1963, Naimi et al. 1963, Mackay and Hume 1964, Charkabarti et al. 1966).

SUMMARY

The euglobulin lysis time before and after moderate exercise and before and after intravenous adrenaline has been studied in normal subjects between the ages 18-30 years. The resting euglobulin lysis time varied from subject to subject and from day to day in the same subject. There was a highly significant lower level in the females. There was no correlation in the resting levels of euglobulin lysis time with the menstrual cycle.

The fibrinolytic reactivity to moderate exercise and intravenous adrenaline was reproducible in anyone individual, but there was significant difference in reactivity between individuals, which revealed the presence of a group of consistently poor reactors. The fibrinolytic reactivity in women, of the same age group, was significantly greater than men, but there appeared to be no changes coincident with the phases of the menstrual cycle.

The possible significance of these findings are discussed in the light of Astrup's hypothesis of the aetiology of atherosclerosis and/or thrombosis.

RESULTS

TABLE I.

Euglobulin Lysis Time before and after moderate exercise in male and female subjects between 18 - 30 years.

MALES					FEMALES				
Subject No.	Euglobulin Lysis Time		% Increase	Mean % Increase	Subject No.	Euglobulin Lysis Time		% Increase	Mean % Increase
	Before	After				Before	After		
M 1	140	71	49		F 1	156	71	54	
	660	332	50	49		228	100	56	54
	500	257	49			198	95	52	
M 2	240	110	54		F 2	112	70	38	
	304	136	55	55		113	75	34	39
						99	62	37	
						97	61	37	
M 3	195	120	48		F 3	115	55	50	
	105	58	45			88	45	49	48
	135	80	40	43		177	96	46	
	77	45	42			140	74	47	
	83	51	39						
	148	92	38						
M 4	620	440	29		F 4	117	49	58	
	84	60	29			425	117	73	65
	270	200	26	29		120	45	63	
	318	213	33						
	210	156	26						
M 5	61	35	43		F 5	160	83	48	
	75	42	44			200	100	50	49
	57	35	39	37					
	65	45	31						
	81	50	38						
M 6	115	70	39		F 6	222	97	56	
	146	96	34	37		135	71	47	
						204	90	56	52
						192	95	51	
						193	97	50	
						143	70	51	
M 7	105	60	43		F 7	102	48	53	
	131	78	41	39		141	65	54	52
	77	47	39			90	45	50	
	76	50	34						
M 8	550	440	20		F 8	132	53	60	
	211	172	19	24		370	134	64	64
	745	505	32			300	100	67	
M 9	143	60	58		F 9	132	57	57	
	150	65	57	58		135	62	54	53
	150	62	59			117	50	47	
						95	45	53	

M A L E S (CONT)					F E M A L E S (CONT.)				
M 10	105	63	40		F 10	84	43	49	
	95	59	38	40		77	42	45	48
	103	60	42			80	41	49	
M 11	255	124	51		F 11	123	72	42	
	315	153	51	51		131	75	43	42
	262	129	51			132	74	44	
						120	75	38	
M 12	120	95	21		F 12	132	62	53	
	159	116	27			135	65	52	51
	272	192	29	26		145	71	51	
	151	106	30			142	62	49	
	245	185	24						
	132	98	26						
M 13	494	211	57		F 13	180	92	49	
	720	370	48	52		306	142	54	52
	274	137	50			250	117	53	
						148	71	52	
M 14	100	54	46		F 14	595	380	36	
	113	56	50	50		185	110	41	39
	110	52	53			90	53	41	
M 15	112	52	54		F 15	105	45	57	
	223	104	53	54		110	55	50	51
	180	80	56			100	50	50	
						105	55	48	
M 16	257	143	44		F 16	115	95	48	
	120	80	33	38		138	81	41	43
	140	90	36			171	101	41	
M 17	72	65	10		F 17	150	76	49	
	108	86	20			198	93	51	47
	200	184	8	11		178	87	45	
	320	310	3			178	95	41	
M 18	189	99	48	49	F 18	166	85	49	44
	270	137	49			176	104	41	
						162	95	42	
M 19	65	51	22		F 19	176	103	42	
	84	56	33	29		202	124	39	40
	94	64	32			200	120	40	

M A L E S (CONT.)					F E M A L E S (CONT.)				
M 20	250	160	36	36	F 20	121	68	43	
	230	150	35			131	73	44	44
						117	65	44	
M 21	116	87	25		F 21	68	30	56	
	108	82	24	24		80	33	59	
	110	85	23			82	32	56	56
						89	39	54	
M 22	120	75	38		F 22	90	45	50	
	500	300	40	39		105	53	50	50
T						112	58	49	
M 23	174	89	49		F 23	115	60	48	
	135	77	43	44		107	60	44	46
	100	60	40						
M 24	539	324	40		F 24	99	52	47	
	269	162	40	40		96	56	42	45
						110	61	45	
M 25	107	63	42		F 25	118	73	38	38
	76	45	41	40		120	74	38	
	95	60	37						

TABLE 2.

Euglobulin Lysis Times before and after moderate exercise in 9 female subjects during a menstrual cycle.

SUBJECT NO.	EUGLOBULIN LYSIS TIME BEFORE	AFTER	% INCREASE
F 6	222	97	56
	135	71	47
	204	90	56
	* 192	95	51
	193	97	50
	143	70	51
F 2	112	70	38
	113	75	34
	* 99	62	37
	97	60	37
F 3	115	55	50
	88	45	49
	177	96	46
	* 140	74	47
F 9	132	57	57
	* 135	62	54
	117	50	47
	95	45	53
F 11	123	72	42
	131	75	43
	* 132	74	44
	120	75	38
F 12	132	62	53
	* 135	65	52
	145	71	51
	142	62	49
F 15	105	45	57
	110	55	50
	100	50	50
	* 105	55	48
F 17	150	76	49
	198	93	51
	* 178	87	45
	178	95	41
F 21	68	30	56
	80	33	59
	* 82	32	56
	89	39	54

* Results during menstruation.

TABLE 3.

The mean percent response in euglobulin lysis time and pulse rate increase following moderate exercise in 13 males and 9 females.

MALES				FEMALES			
SUBJ. NO.	MEAN % RESPONSE (E.L.T.)	PULSE RATES BEFORE & AFTER	PULSE RATE RESPONSE	SUBJ. NO.	MEAN % RESPONSE (E.L.T.)	PULSE RATES BEFORE & AFTER	PULSE RATE RESPONSE
M 1	49	75 - 152	77	F 1	54	63 - 149	86
M 2	55	59 - 120	61	F 2	39	60 - 130	70
M 3	43	85 - 150	65	F 4	65	80 - 160	80
M 4	29	71 - 148	77	F 7	52	73 - 161	88
M 5	37	62 - 136	74	F 8	64	72 - 161	89
M 8	24	83 - 148	65	F 9	53	63 - 159	96
M 12	26	71 - 138	67	F 10	48	71 - 165	94
M 13	52	71 - 142	71	F 13	52	67 - 154	87
M 14	50	69 - 136	67	F 15	51	81 - 148	67
M 15	54	72 - 124	52				
M 16	38	84 - 156	72				
M 17	14	60 - 143	83				
M 21	24	51 - 136	85				
			Mean=70				Mean=84

TABLE 4.

The euglobulin lysis time before and 2 minutes after intravenous adrenaline in 25 subjects aged 18 - 30 years.

MALES					FEMALES				
Subject No.	Euglobulin Lysis Time		% Increase	Mean % Increase	Subject No.	Euglobulin Lysis Time		% Increase	Mean % Increase
	Before	After				Before	After		
M. 1.	165	68	61		F. 1	103	43	60	
	104	48	54	58		111	47	58	59
						150	60	60	
M. 4	210	113	46	46	F. 2	100	55	45	45
M. 6	107	62	41	41	F. 3	120	52	57	
						90	40	56	57
M. 8	565	510	9		F. 6	120	55	54	
	655	505	22	18		122	57	53	53
						105	51	51	
M. 9	250	90	65	65	F. 11	109	54	50	54
						119	53	56	
						140	62	55	
M. 10	125	71	43		F. 12	143	56	58	56
	56	32	43	43		104	59	54	
M. 12	270	185	32	37	F. 13	237	147	39	
	160	92	42			290	150	36	40
						151	81	46	
M. 15	91	32	65	65	F. 14	139	57	59	
						122	56	54	57
M. 17	97	57	41		F. 15	126	45	66	
	80	56	30	35		117	57	51	58
						95	42	56	
M. 18	150	55	63		F. 17	126	48	62	
	113	48	59	61		101	46	55	57
						120	44	55	
M. 19	86	46	46		F. 21	77	49	37	
	83	45	45	45		54	37	32	36
	73	40	47			54	33	39	
M. 21	105	60	42						
	98	58	41	42					
M. 23	88	46	48						
	140	70	50	48					
	96	50	47						
	215	103	50						
M. 26	92	37	59						
	134	46	65						
	115	40	65	62					
	140	45	60						

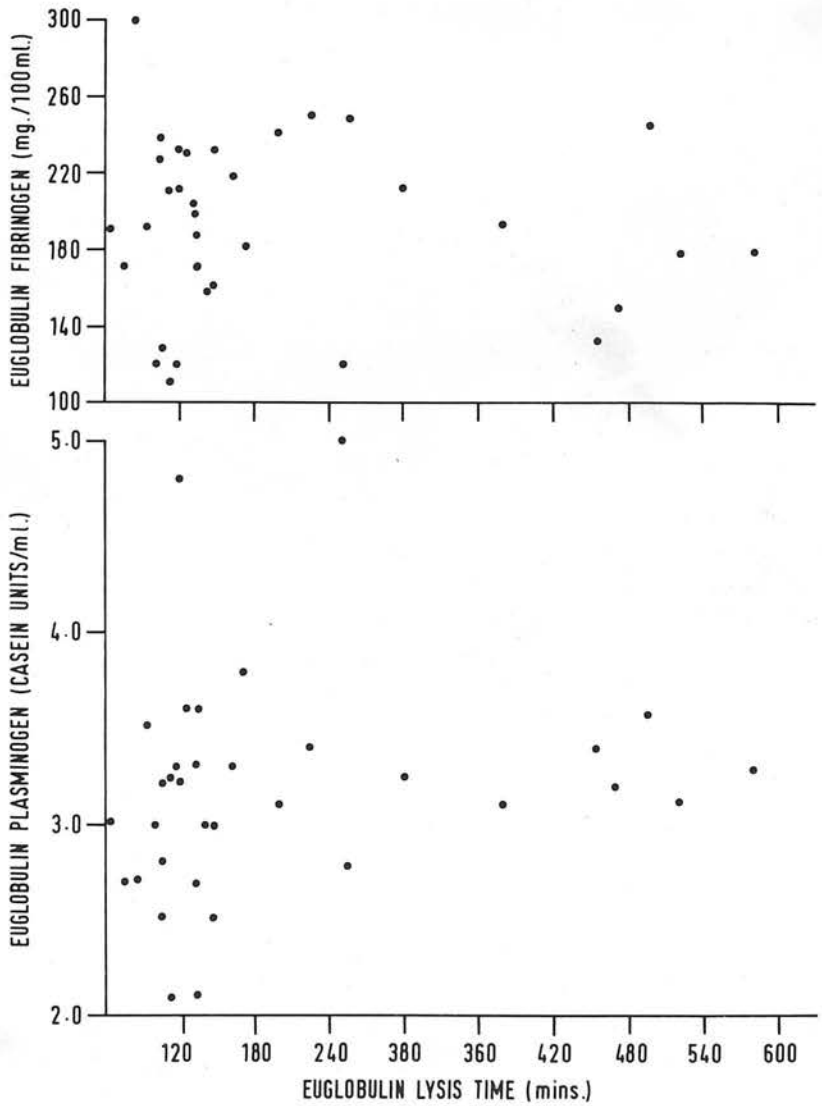

FIG.1. EUGLOBULIN PLASMINOGEN AND FIBRINOGEN PLOTTED AGAINST THE EUGLOBULIN LYSIS TIME.

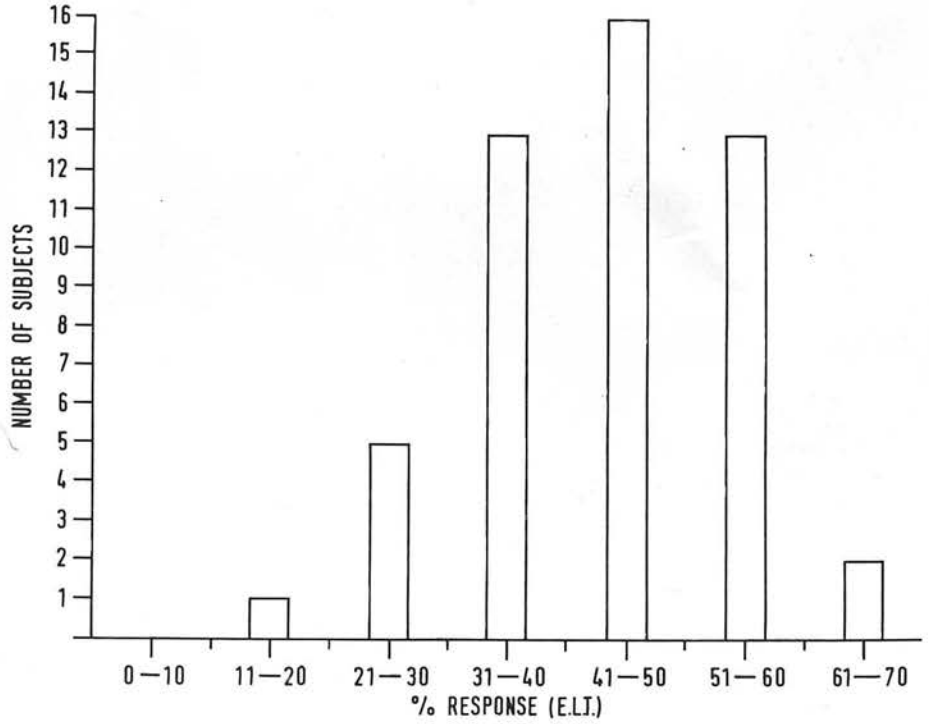

FIG. 2. FREQUENCY DISTRIBUTION OF PERCENT RESPONSE TO MODERATE EXERCISE IN ALL SUBJECTS.

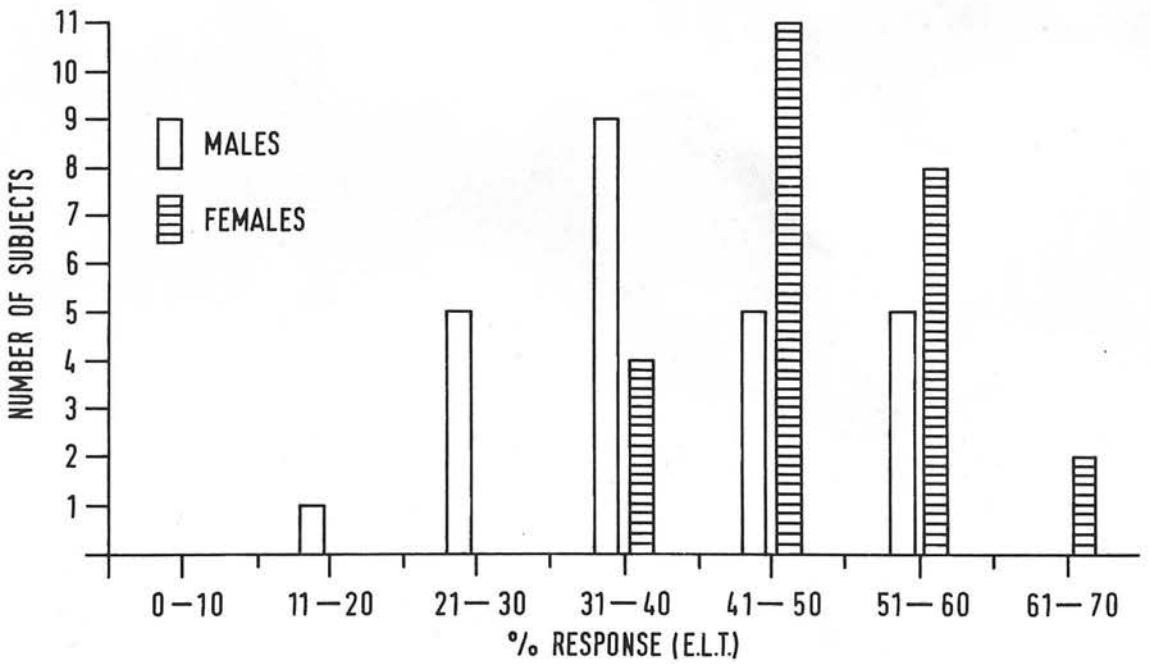

FIG. 3. FREQUENCY DISTRIBUTION OF PERCENT RESPONSE TO MODERATE EXERCISE IN MALES AND FEMALES.

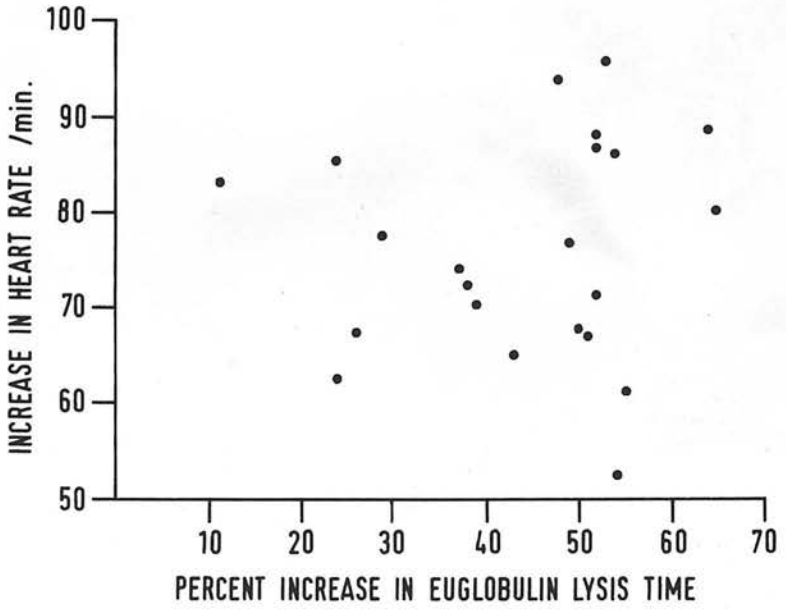

FIG. 4. PERCENT INCREASE IN EUGLOBULIN LYSIS TIME PLOTTED AGAINST INCREASE IN HEART RATE, FOLLOWING MODERATE EXERCISE.

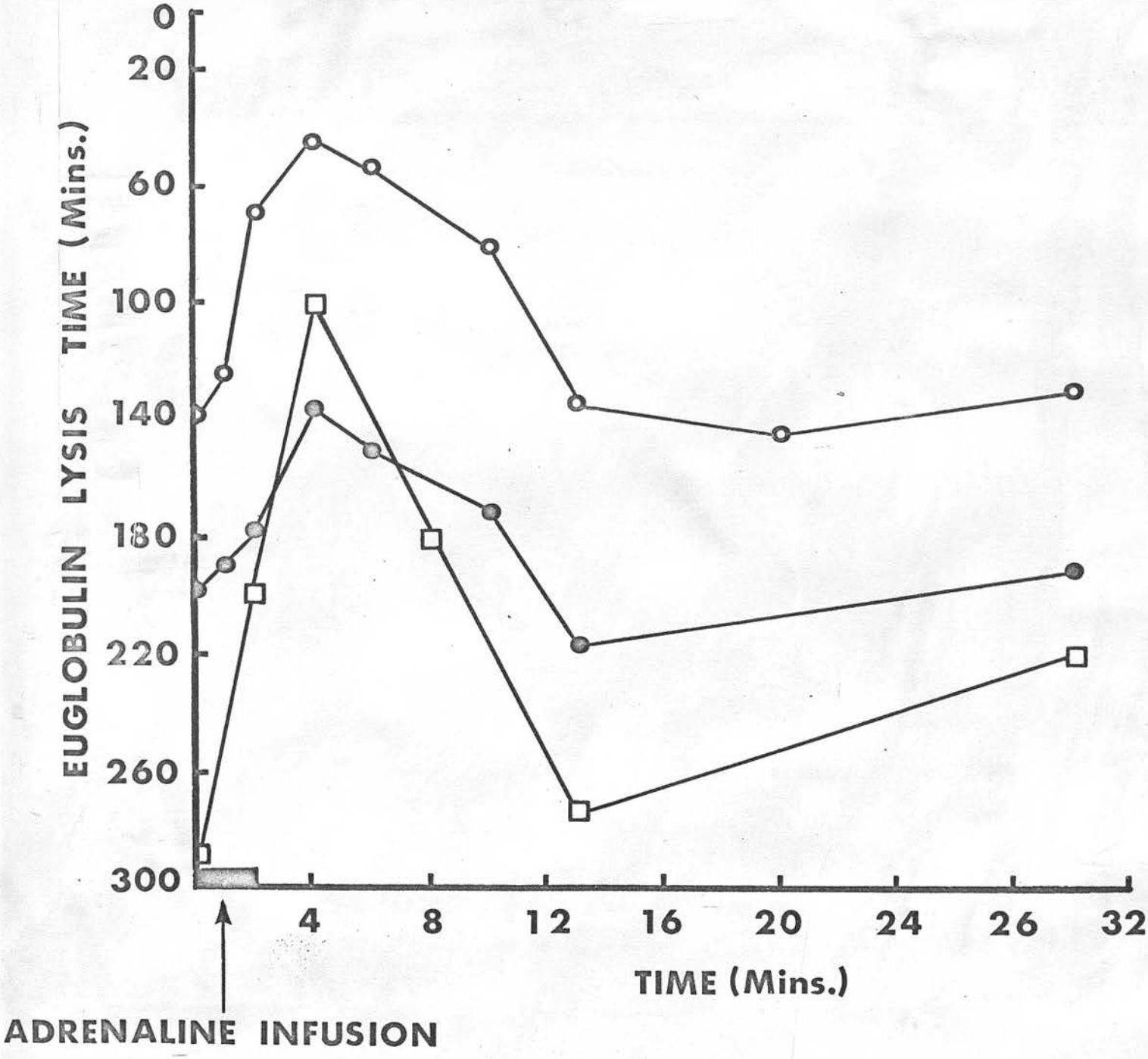

Fig. 5.

The fibrinolytic response to intravenous adrenaline in 3 subjects.

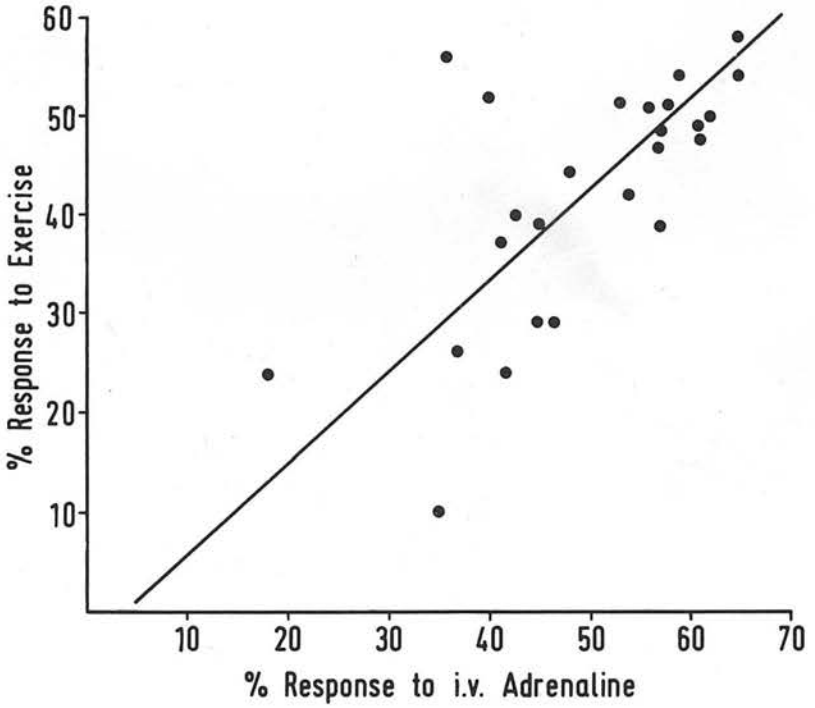

Fig. 6. Correlation between the percent increase in euglobulin lysis time to moderate exercise and i.v. adrenaline.

$r = 0.855$, $p < 0.001$, $y = -3.4 + 0.92x$

REFERENCES

Alkjaersig, N, Fletcher, A. P., and Sherry, S. (1959) J. Clin. Invest. 38, 1086.

Alkjaersig, N. (1960) In: Roberts, H. R. and Geratz, J. D. ed. Proceedings of the Conference on Thrombolytic Agents, April 8-9, 1960, Chicago, Illinois, p. 136. (The Haematology Study Section, (U.S.) Public Health Service.

Ambrus, J. C., Simpson, C. L., Shulman, S. (1958) J. Clin. Invest. 37, 864.

Astrand, P-O (1952) Experimental Studies of Working Capacities in Relation to Sex Age. Copenhagen. Munksgaard.

Astrup, T. (1956) Lancet, 2, 565.

Beller, F. K., Goebelsmann, U., Douglas, G. W. and Johnson, A. (1964). Obstet. and Gynec. 23, 12.

Biggs, R., Macfarlane, R. G. and Pilling, J. (1947) Lancet, 1, 402.

Billimoria, J. D., Drysdale, J., James, D. D. O.and Maclagan, N. F. (1959) Lancet, 2, 730.

Bond, T. P., Celander, D. R. and Guest, M. M. (1961) Fed. Proc. 20, 56.

Blix, S. (1961) Scand. J. Clin. Lab. Invest. 13, Suppl. 58, 11.

Blix, S. (1964) Scand. J. Clin. Lab. Invest. 16, 403.

Blomback, B. and Blomback, M. (1956) Ark. Kemi. 10, 415.

Brakman, P., Albrechtsen, O. K. and Astrup, T. (1966) Brit. J. Haemat. 12, 74.

Burt, J. J., Blyth, C. S. and Rierson, H. A. (1964) J. Sport, Medecine and Physical Fitness (Torino) 4, 213.

Chakrabarti, R., Fearnley, G. R., Hocking, E. D., Dettheos, A. and Clarke, G. M. (1966) Lancet, 1, 573.

Copley (1954) Arch. int. Pharmacodyn, 99, 426.

Copley (1957) Lancet, 1, 102.

Crawford, T. and Levene, C. (1952) J. Path. Bact. 64, 523.

Doni, A., Palchetti, R., Bolletti, A. and Vernaglione (1963) Riv. Crit. Clin. Med., 63, 5.

Dreyfuss, F. (1956) J. psychosom. Res. 1, 252.

Duguid, J. B. (1948) J. Path. Bait. 60, 57.

Duguid, J. B. (1949) Lancet, 2, 925.

Duguid, J. B. (1955) Brit.Med. Bull., 11, 36.

Euler, U. S. and Hellner, S. (1952). Acta. physiol. Scand. 26, 183.

Fearnley, G. R., Lackner, R. (1955) Brit. J. Haemat., 1, 189.

Fearnley, G. R. (1959) Lancet 2, 1067.

Fearnley, G. R. (1961) Lancet 1, 992.

Fearnley, G. R. (1965) Fibrinolysis. Edward Arnold (Publishers) Ltd.

Fletcher, A. P., Bierderman, O., Moore, D., Alkjaersig, N. and Sherry, S. (1964) J. clin. Invest. 43, 681.

Friedman, M., Rosenman, R. H. and Carroll, V. (1958) Circulation, 17, 852.

Genton, E., Kern, F., von Kaulla, K. (1961). Amer. J. Med. 31, 564.

Grant, W. C., Wasserman, F., Rodensky, P. C. and Thomson, R. V. (1959) Ann. internat. Med. 51, 774.

Harrison, C. V. (1948) J. Path. Bact. 60, 289.

Hend, B. E. (1949) J. Path. Bact. 61, 635.

Holman, R. L., McGill, H. C., Strong, J. P. and Geer, J. C. (1958) Amer. J. Path. 34, 209.

Holmgren, A. (1956) Scand. J. clin. Lab. Invest. 8, suppl. 24, 1.

Howell, W. and Manion, W. C. (1960) Amer. Heart. J. 60, 341.

Hume, R. (1958) Brit. Heart. J. 20, 15.

Iatridis, S. G. and Ferguson, J. H. (1963) J. appl. Physiol. 18, 337.

Jange, E., Fletcher, B. T. and Bickford, A. F. (1964) Clin. Sci. 27, 9.

Katz, A. M., McDonald, L., Davies, B. and Edgill, M. (1963) Lancet, 1, 801.

Von Kaulla, K. N. and von Kaulla, E. (1964) Circ. Res. 14, 436.

Lackner, H. and Merskey, C. (1960) Brit. J. Haemat. 6, 402.

Macfarlane, R. G. and Briggs, R. (1948) Blood, 3, 1167.

Macht, D. I. (1952) J. Amer. Med. Ass. 148, 265.

Mackay, N. and Hume, R. (1964) Scot. med. J. 9, 359.

Naimi, S., Goldstein, R. and Proger, S. (1963) Circulation, 27, 904.

Nestel, P. J. (1960) Anst. Ann. Med. 9, 234.

Nolf, P. (1908) Arch. int. Physiol. 6, 306.

Ogston, D. (1962) Brit. Med. J. 1, 1242.

Ogston, D. and Fullerton, H. W. (1961) Lancet, 2, 730.

Ogston, D., McDonald, G. A. and Fullerton, H. W. (1962) Lancet, 2, 521.

Ogston, D. and McAndrew, G. M. (1964) Lancet, 2, 1205.

Ollendorff, P., Rasmussen, P. and Astrup, T. (1966) Acta. med. Scand. 179, 101.

Owren, P. A. (1947) Acta. med. Scand. Suppl. 194.

Ratnoff, O. D. and Menzie, C. A. (1951) J. Lab. Clin. Med. 37, 316.

Remmert, C. F. and Cohen, P. P. (1949) J. biol. Chem. 181, 431.

Rokitansky, C. (1842) "Handbuch der Pathologischen Anatomie", V.3.
Braumeller and Seidel.

Roos (1958) Thrombos. Diathes. haemorrh. (Stuttg.) 1, 471.

Salmon, J. (1961) C. R. Soc. Biol. (Paris) 155, 1159.

Sawyer, W. D., Fletcher, A. P., Alkjaersig, N. and Sherry, S. (1960)
J. clin. Invest. 39, 426.

Sherry, S., Lindemyer, R. I., Fletcher, A. P. and Alkjaersig, N. (1959)
J. clin. Invest. 38, 810.

Strong, J. P. and McGill, H. C. (1962) Amer. J. Path. 40, 37.

Tanser, A. R. and Smellie, H. (1964) Clin. Sci. 26, 375.

Thomas, W. A. (1957) Nutr. Dev. 15, 97.

Truelove, S. C. (1951) Clin. Sci. 10, 229.

Vendsalu, A. (1960) Acta. Physiol. Scand. Suppl. 173.

Vuori, J. (1950) Acta. med. Scand. 236, 296.

Weiner, M. (1963) Amer. J. Med. Sci. 246, 295.