(Barabas, 1966), varicose veins (Sæmundsson, 1956), and rupture of large arteries (McFarland and Fuller, 1964), are well-documented manifestations in this syndrome.

However, this study is the first attempt to analyse the distribution of the different varieties and complications in a considerable number of patients. It has been shown that the same clinical picture appears in affected members of each family, and that certain clinical signs and complications regularly occur together. These observations gain practical importance, especially when applied to the group with the only potentially fatal complications of Ehlers-Danlos syndrome—the rupture of large arteries.

Arterial rupture as a complication of Ehlers-Danlos syndrome was first reported by Mories (1960). Since then at least six further examples have been described (McFarland and Fuller, 1964; Lynch *et al.*, 1965; André *et al.*, 1965; McKusick, 1966). Except in two patients (André *et al.*, 1965; Lynch *et al.*, 1965), the diagnosis of Ehlers-Danlos syndrome was made retrospectively after the fatal arterial rupture.

The present series is unique because it includes two patients who survived several arterial ruptures. They were compared with 25 patients without a history of arterial rupture. Though the two patients showed clinical and histological features well within the present definition of Ehlers-Danlos syndrome, they differed from the 25 in important aspects such as their liability to gross bruising, the peculiar transparency of their skin, the minor degrees of skin hyperextensibility and joint hypermobility, and their attacks of severe abdominal pain.

It is suggested, therefore, that Ehlers-Danlos syndrome with arterial complications should be regarded as a separate entity, and an impending arterial catastrophe need not be anticipated in those patients differentiated in groups 1 and 2 above.

Basic Defect

The basic defect in Ehlers-Danlos syndrome has long been, and still is, a matter for argument. Most investigators think that it lies in the collagen (McKusick, 1966), but others believe it is a primary elastic-fibre defect (Goltz and Hult, 1965). Wechsler and Fisher (1964) showed convincingly that there are no microscopical or electron-microscopical defects in either fibre. Jackson and Bentley (1967) suggested that the defect in

Ehlers-Danlos syndrome lies at a high level of organization of the collagen fibres. Their hypothesis is an elaboration of Jansen's (1955) defective collagen "wickerwork" theory. According to them, in this high-level binding the collagen fibrils interact with the various mucopolysaccharides and mucopolysaccharide-protein complexes of the "ground substance."

In the three types of Ehlers-Danlos syndrome three different mucopolysaccharides or mucopolysaccharide-protein complexes may be at fault. All three would lead to some bruising and scarring of the skin and to some joint hypermobility; but each defect would cause a specific weakness, such as the gross capillary and arterial wall fragility in the "arterial" type.

Summary

Twenty-seven patients with Ehlers-Danlos syndrome belonging to 15 families were examined. Three distinct familial clinical types were found—"classical," "varicose," and "arterial."

A new hypothesis regarding the basic defect(s) in Ehlers-Danlos syndrome is discussed.

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REFERENCES

- André, R., Duhamel, G., Vergoz, D., and Lavallée, R. (1965). *Bull. Soc. méd. Hôp. Paris*, **116**, 971.
 Barabas, A. P. (1966). *Brit. med. J.*, **2**, 682.
 Goltz, R. W., and Hult, A. M. (1965). *Sth. med. J. (Bgham, Ala.)*, **58**, 848.
 Jackson, D. S., and Bentley, J. P. (1967). *Collagen*, vol. 2, edited by B. S. Gould. London. In press.
 Jansen, L. H. (1955). *Dermatologica (Basel)*, **110**, 108.
 Lynch, H. T., Larsen, A. L., Wilson, R., and Magnuson, C. L. (1965). *J. Amer. med. Ass.*, **194**, 1011.
 McFarland, W., and Fuller, D. E. (1964). *New Engl. J. Med.*, **271**, 1309.
 McKusick, V. A. (1966). *Heritable Disorders of Connective Tissue*, 3rd ed. St. Louis.
 Mories, A. (1960). *Scot. med. J.*, **5**, 269.
 Sæmundsson, J. (1956). *Acta med. scand.*, Suppl. No. 312, vol. 154, p. 399.
 Wechsler, H. L., and Fisher, E. R. (1964). *Arch. Path.*, **77**, 613.

Preliminary Communications

Increased Fibrinolytic Activity in Venous Blood of Hemiplegic Limbs

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In a study of fibrinolysis in the venous blood from hemiplegic patients an increased rate of fibrinolysis was observed in the blood obtained from the hemiplegic limb compared with that from the contralateral side.

MATERIAL AND METHODS

Forty-seven estimations of euglobulin lysis time (E.L.T.) and 44 estimations of dilute blood clot lysis time (D.B.C.L.T.) were made on 21 consecutive hemiplegic patients admitted to an acute medical ward. Blood was collected by clean venepuncture with minimal stasis from both arm veins between 9 and 9.30 a.m. The patients were in bed and had had their

breakfast. In 21 estimations blood was collected first from the hemiplegic arm and in the remainder first from the non-hemiplegic arm. Samples of 4.5 ml. of blood were immediately mixed with 0.5 ml. of 3.8% sodium citrate contained in chilled test-tubes. These were subsequently spun at approximately 1,500 r.p.m. for seven minutes, the centrifuge buckets for the plasma tubes having previously been cooled at 0° C. All blood and plasma specimens were kept in melting ice, and tests were carried out within 30 minutes of obtaining the specimen. The euglobulin lysis time was then estimated by the method of von Kaulla (1963), slightly modified as follows: (1) all the procedures previous to the incubation of the clot were carried out at 0° C., (2) after passage of CO₂ the tubes were centrifuged for four minutes, and (3) euglobulin was clotted by the addition of 1 ml. of thrombin solution (2 units).

All estimations were made in duplicate. The dilute blood clot lysis time was estimated by the method of Fearnley *et al.* (1957), a camera being used to determine the end-point as described by Lackner and Goosen (1959).

RESULTS

Evidence of increased fibrinolysis was found in the venous blood obtained from the hemiplegic arm as compared with that from the normal arm in all but one estimation of euglobulin lysis time and in all four estimations of dilute blood clot lysis time. It is noteworthy that in the only case where there was no difference in the euglobulin lysis time between the two arms the lysis time was 20 minutes. At this rapid rate of lysis small differences are easily overlooked, and it is possible that this was the case in the four estimations of dilute blood clot lysis time where no difference was observed, especially since the automatic camera records only every half-hour and differences of less than 30 minutes in the lysis time are thus not registered. On only one occasion did the non-paralysed arm have a faster lysis time than the paralysed as shown by the dilute blood clot lysis time, and it should be stressed that a simultaneous euglobulin lysis time reading was not in agreement. The significance of the differences in the lysis time between the two arms is therefore not in doubt.

The Table shows the lysis time in relation to the duration of the hemiplegia in the different patients; this varied from one

Lysis Times

Case No.	Age and Sex	Side of Hemiplegia	No. of Days from Onset	E.L.T. in mins.			D.B.C.L.T. in mins.		
				Hemiplegia	Normal	Difference	Hemiplegia	Normal	Difference
1	62 F	R	11	245	255	10	360	420	60
2			21	155	275	120	330	480	150
3			36	130	140	10	660	840	180
4			44	125	140	15	360	450	90
5	61 M	R	6	360	400	40	540	600	60
6			11	115	190	75	240	300	60
7			13	300	360	60	720	720	0
8			24	420	480	60	960	1,440	480
9	46 M	R	32	195	240	45	150	305	155
10			2	330	360	30	360	420	60
11			23	115	135	20	360	420	60
12			3	240	250	10	270	360	90
13	72 M	L	17	60	130	70	100	135	35
14			1	20	250	180	330	540	210
15			4	20	20	0	330	330	0
16			1	270	450	180	390	390	0
17	80 F	R	12	45	55	10	55	80	25
18			13	80	125	45	60	90	30
19			1	140	165	25	420	420	0
20			3	450	480	30	Not done	Not done	0
21	53 M	R	8	335	390	55	1,020	1,200	180
22			4	200	245	45	390	540	150
23			2	200	360	160	540	600	60
24			6	230	360	130	480	540	60
25	58 M	L	1	60	90	30	300	420	120
26			3	120	135	15	360	420	60
27			8	135	165	30	420	510	90
28			13	80	90	10	240	270	30
29	68 F	R	2	420	540	120	1,440	1,560	120
30			5	210	225	15	265	320	55
31			2	180	205	25	360	480	120
32			7	465	495	30	360	540	180
33	74 M	R	9	100	460	360	210	300	90
34			26	135	165	30	480	540	60
35			36	185	250	65	480	660	180
36			42	160	540	380	200	600	400
37	62 M	L	43	140	160	20	Not done	Not done	0
38			50	160	270	110	390	540	150
39			55	190	270	80	420	600	180
40			8	190	215	25	—	—	—
41	85 M	R	5	100	110	10	210	240	30
42			7	100	140	40	420	480	60
43			11	90	105	15	330	360	30
44			3	190	390	200	300	360	60
45	62 F	L	12	115	140	25	195	225	30
46			10 months	110	135	25	Not done	Not done	0
47			2 years	125	190	65	270	540	270
48									
Mean	65			183	250	67	397	502	102

The total figures for each patient give a higher figure for the normal than for the hemiplegic limb, which is statistically very highly significant, by both E.L.T. ($P < 10^{-5}$) and D.B.C.L.T. methods ($P < 10^{-5}$).

day to two years. It also shows serial estimations of individual patients from the time of onset of the condition, but no consistent pattern could be demonstrated.

DISCUSSION

Increased fibrinolytic activity has been reported in a large number of different conditions, such as states of shock occurring

after trauma and severe burns, after strenuous exercise or injections of adrenaline (Franz *et al.*, 1961), in acute leukaemia, and in the presence of metastatic carcinoma (Steichele and Herschlein, 1962). In the present context, however, alterations either in the nervous control of the vascular endothelium or in the circulatory haemodynamics seem much more likely to be relevant.

In the normal human fibrinolytic system a labile activator is produced by the endothelium of the veins (Messer *et al.*, 1962) and liberated into the blood stream, where it reacts with plasminogen to form plasmin. The factors which control the rate of this liberation have not yet been completely clarified, but the fact that venous stasis by tourniquet leads to a marked increase in the fibrinolytic activity in the blood within the vein suggests that the rate of the flow largely determines how much of the activator any aliquot of blood will pick up per unit time. In a hemiplegic limb either of the two variables mentioned might be affected.

The known effect of adrenaline in accelerating fibrinolysis raised the question of whether autonomic control of the hemiplegic limb would provide an explanation for the accelerated fibrinolysis. Kwann *et al.* (1957) suggested that such autonomic nervous control of fibrinolysis might exist, and the experimental work of Sherry *et al.* (1959) supports this theory. That the autonomic control of a limb is disturbed by a hemiplegia is confirmed by many observations, ranging from the statement by Brain (1962) that such control is normally exercised by area 13 of the cerebral cortex (which presumably could often be damaged by a cerebral infarction) to the extensive vasomotor changes described by Steinmann (1963). The sympathetic nerves have adrenergic and cholinergic components, both of which appear to be affected by a hemiplegia though to a degree which seems to vary considerably from case to case. Investigation of the effect of a hemiplegia on the mechanism of sweating (mainly a cholinergic effect) showed that sweating in response to subcutaneous injections of pilocarpine was greater on the hemiparetic side in three patients and on the normal side in two patients, but in most there was very little difference. The characteristic feature, however, of the present study of fibrinolytic activity is the constancy of the increase on the hemiparetic side irrespective of the duration of the hemiplegia.

Consequently it seemed more likely that changes in the fibrinolytic activity would be related to the rate of the blood flow in the veins from which the blood was withdrawn. Contradictory reports of how the hemiparesis affects the rate of the blood flow have appeared in the literature. Ellis and Weiss (1936), for instance, showed by plethysmographic techniques that the blood flow through the paretic limb was increased and might remain so for as long as 13 years, while LaBan and Johnson (1965), using a cutaneous thermal indicator technique, found that the velocity of the venous blood flow was markedly reduced, usually by 50% or more. Probably the blood flow through the deep vessels is rapid, travelling from arteries to veins by shunts which avoid the capillaries of the inactive muscles (Hoerner *et al.*, 1964), while on the surface the flow through the veins is consistently slow. Thus the slow flow would allow more time for the activator to be released into the blood, which would explain the acceleration of the fibrinolytic activity.

Since the rate of flow through the superficial veins of the limb appears to reflect fairly closely the motor activity of the muscles underneath, it is hardly surprising that it is less on the hemiparetic side. There may of course be other explanations, and it would be of great interest to compare the fibrinolytic activity of the blood in the superficial veins with that in the deep veins of the hemiplegic limb. The advantage to the organism of having an increased fibrinolytic activity in a sluggish circulation is obvious and the reason why this protective mechanism occasionally fails is one of the challenging problems of our time.

SUMMARY

Increased fibrinolytic activity in the blood of the superficial veins of hemiplegic arms as compared with that in the same veins on the normal side was observed in 20 out of 21 patients studied in whom hemiplegia had been present for up to two years. Possible explanations for this are discussed.

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REFERENCES

- Brain, Lord (1962). *Diseases of the Nervous System*, 6th ed., p. 768. London.
- Ellis, L. B., and Weiss, S. (1936). *Arch. Neurol. Psychiat. (Chic.)*, **36**, 362.
- Fearnley, G. R., Balmforth, G., and Fearnley, E. (1957). *Clin. Sci.*, **16**, 645.
- Franz, R. C., Kark, A. E., and Hathorn, M. (1961). *Lancet*, **1**, 195.
- Hoerner, E. F., Dasco, M. M., McKeown, J., and Case, H. (1954). *Angiology*, **5**, 414.
- Kwaan, H. C., Lo, R., and McFadzean, A. J. S. (1957). *Clin. Sci.*, **16**, 241.
- LaBan, M. M., and Johnson, E. W. (1965). *Arch. phys. Med.*, **46**, 245.
- Lackner, H., and Goosen, C. C. (1959). *Acta haemat. (Basel)*, **22**, 58.
- Messer, D. L., Celander, D. R., and Guest, M. M. (1962). *Circulat. Res.*, **11**, 832.
- Sherry, S., Lindemeyer, R. I., Fletcher, A. P., and Alkjaersig, N. (1959). *J. clin. Invest.*, **38**, 810.
- Steinmann, B. (1963). *Schweiz. med. Wschr.*, **93**, 172.
- Steichle, D. F., and Herschlein, H. J. (1962). *Med. Welt*, **3**, 141.
- von Kaulla, K. N. (1963). *Chemistry of Thrombolysis: Human Fibrinolytic Enzymes*, p. 79. Springfield, Illinois.

Medical Memoranda

Paracetamol and the Kidney

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Phenacetin had been used for many decades before its nephrotoxic properties were recognized (Spühler and Zollinger, 1953). Because of the general belief that paracetamol is safe, it has become a popular substitute, but hepatic damage with disturbance of glucose metabolism has now been reported (Davidson and Eastham, 1966; Thomson and Prescott, 1966). The following case suggests that it can also cause renal lesions. It was taken in the form of a proprietary preparation (Beserol, Lobak), which contains paracetamol 450 mg. and chlormezanone 100 mg. in each tablet.

CASE HISTORY

A 45-year-old European man underwent partial gastrectomy for duodenal ulcer in 1962, and was given Beserol for wound pain; he took two to four tablets a day for two months. Ten months later he again started Beserol, now because of "sinus headaches" and nervous tension, but in vast quantities—12 tablets a day for four months, followed by 25 to 40 (average 30) daily for another six months. When this was realized Beserol was stopped and the tension treated with chlordiazepoxide 15 mg. daily. Seven months later he developed right loin pain and passed blood and fragments of tissue in the urine. An intravenous pyelogram showed no excretion of contrast medium, and he was admitted to the Salisbury Central Hospital on 2 September 1965.

He denied having taken other analgesics, apart from an occasional aspirin or proprietary compound tablet for headache.

Examination revealed a thin sallow man with no loin tenderness or other physical abnormality; the blood pressure was 135/85 mm. Hg. The urine was acid and contained neither protein nor glucose; microscopy disclosed numerous red and white blood cells but no casts, ova, or crystals; three specimens were sterile, and there were no acid-fast bacilli. The haemoglobin was 11.4 g./100 ml., white cells 7,500/cu. mm., and differential count and film normal. The postprandial blood glucose was 110 mg./100 ml. on two separate occasions, and the blood urea was 130 mg./100 ml.; serum electrolytes and proteins were normal. There was no methaemoglobinaemia or sulphaemoglobinaemia.

Cystoscopy (Mr. R. M. Honey) was normal apart from haemorrhages surrounding the right ureteric orifice. Retrograde

pyelograms: both kidneys were unduly small (10 cm. long), with signs of papillary necrosis on the right (Fig. 1) but not on the left (Fig. 2).

FIG. 1

FIG. 2

FIG. 1.—Retrograde pyelogram showing small right kidney; upper and middle calices are clubbed, with some leakage of contrast medium into renal substance. FIG. 2.—Retrograde pyelogram showing small left kidney, but apparently normal caliceal system.

On a low-protein diet the blood urea fell to 54 mg./100 ml. during the next three weeks; serum creatinine 3.5 mg./100 ml., creatinine clearance 25 ml./minute. He was discharged from hospital but did not return for follow-up, though six months later he was back at work and apparently well.