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MEDICAL MEMORANDA

Idiopathic Gangrene in African Adults

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Idiopathic peripheral limb gangrene in African adults and children is a well-recognized clinical entity (Turpie *et al.*, 1967), and little evidence of a cause has been found (Bhana and Baddeley, 1970). We have defined abnormalities in the blood coagulation and fibrinolytic enzyme systems in two such adult patients which may offer a possible explanation for the clinical manifestations of the disease.

Present Series

Venous samples were collected in 3·8% sodium citrate (blood: citrate 9:1) and centrifuged at 1,200 *g* for 10 min at 4°C. Thereafter the supernatant plasma was removed and was either tested immediately or stored at —20°C for further study. Samples for estimation of plasminogen were processed as far as neutralization of pH in the assay procedure and stored for subsequent bulk assay at —20°C. Samples for estimation of fibrinogen and factors V and VIII were delivered in 1-ml aliquots into plastic tubes, each containing 1 mg aminocaproic acid and likewise stored at —20°C for bulk assay. Platelet substitute and rabbit brain thromboplastin (Diagnostic Reagents Ltd.), thrombin (Leo), streptokinase (Kabi), and urokinase (Hoffman-La Roche) were used.

The method of recording euglobulin lysis times is given in the Appendix. All tests of the coagulation and fibrinolytic systems were performed in duplicate. The results are recorded in the Table. The normal results were obtained from 25 healthy African women aged 19-39 years examined by the same techniques in the same laboratory (Barr *et al.*, 1972).

Case 1.—A 30-year-old M'luhya woman was admitted to the Kenyatta National Hospital on 11 February 1971 with a six-month history of intermittent claudication of increasing severity in both legs. Examination on admission showed incipient gangrene of the legs with no palpable lower limb pulses. Sinus rhythm was present and there was moderate hypertension (B.P. 150/110 mm Hg). Physical examination showed no other abnormality. Despite bilateral lumbar sympathectomy and bilateral femoral artery disobliteration, followed by systemic heparinization (intravenous heparin 1.500 U/h), loss of viability of the lower limbs progressed. The patient died suddenly on 1 March while being prepared for amputation. Histological examination of a biopsy specimen of the femoral artery showed recent occlusive thrombus with no abnormality of the vessel wall. At necropsy there was extensive antemortem thrombus in the aorta, both common iliac arteries, and both iliac veins. There was no apparent intrinsic vessel wall disease. A large recent pulmonary embolus was found in the right lung.

Results of Tests on Coagulation and Fibrinolytic Systems

Investigation	Case 1	Case 2	Normal Value
Kaolin-cephalin clotting time (Biggs and MacFarlane, 1966) (sec)	26·5	27·5	40 ± 7·5
One-stage prothrombin time (Douglas, 1962) (sec)	17	16	16 ± 2
Thrombin clotting time (Fletcher *et al.* 1959)* (sec)	6	5	9·5 ± 2·5
Plasma fibrinogen (Ratnoff and Menzies, 1951) (Mg/100 ml)	530	683	295 ± 95
Factor V (Biggs and MacFarlane, 1966)‡ (%)	175	195	103 ± 39
Factor VIII (Biggs and MacFarlane, 1966) (%)	189	189	96 ± 32
Euglobulin lysis time (min)	800	1,440	217 ± 95
Urokinase sensitivity test (McNicol *et al.*, 1963) (sec)	340	388	282 ± 92
Plasma plasminogen (Remmert and Cohen, 1949)† (units)	4·7	5·1	3·9 ± 1·5

* Method of Fletcher *et al.* (1959), with the modification that concentration of thrombin used was 25 U/ml, compared with 10 U/ml in the original method.
† Method of Remmert and Cohen (1949) as modified by Alkjaersig (1960).
‡ Method of Biggs and MacFarlane (1966), with the modification that concentration of calcium chloride used was 0·0125 M.

Case 2.—A 30-year-old Kikuyu woman was admitted to the Kenyatta National Hospital on 19 July 1971 with a history of rapidly progressive gangrene of both legs over a period of 17 days. During that time she had also become incontinent of urine. Examination on admission showed wet gangrene of both legs to the mid-tibial level, with palpable femoral and popliteal pulses. Sinus rhythm was present and she was normotensive. No other abnormality was found. While surgical toilet was being carried out under general anaesthesia on 9 August she died suddenly. At necropsy no definite cause of death was defined. There was bilateral pyonephrosis, with extensive thrombus in the major arteries of the legs in the absence of obvious disease of the vessel wall. The cerebral, coronary, and pulmonary circulations were normal. Histological examination of an arterial biopsy specimen taken from the site of surgical toilet showed recent occlusive thrombus with no abnormality of the vessel wall.

In neither patient was there a history of antecedent illness of any kind known to predispose the vascular disease.

Comment

Turpie *et al.* (1967) described the cases of three children who had idiopathic peripheral gangrene. All showed impaired fibrinolysis as a result of diminished levels of plasma activator and increased levels of inhibitor. The present patients, in addition to having the former abnormality, had raised levels of plasma fibrinogen, factor V, and factor VIII and

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consequent shortening of the kaolin-cephalin clotting time and thrombin time. With such a severe disturbance of the dynamic equilibrium between coagulation and fibrinolysis (Astrup 1956) it is hardly surprising that they suffered extensive thrombotic vascular occlusion. The underlying cause of the imbalance remains undiscovered.

From neighbouring Uganda, however, Bhana and Baddeley (1970) reported on three pregnant women who developed peripheral gangrene after the ingestion of a herbal preparation which is locally supposed to facilitate labour and produce a healthier baby. One of these patients having taken the preparation throughout pregnancy had an arteriographic pattern similar to that produced by ergotism.

In this regard it is of interest that Case 1 presented with a clinical illness compatible with ergotism (Snell and Mukasa, 1948). Furthermore, naturally occurring substances with pronounced antifibrinolytic properties have been known for many years (Tauber *et al.*, 1949). More recently Lipton (1967) described the effect on the uterine and other smooth muscle of laboratory animals of an active glycoside extracted from plants used by East African witch doctors to accelerate labour and procure abortion.

There is clearly a need to search for the possible use of herbal preparations in the pathogenesis of idiopathic gangrene in Africans.

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Appendix

Euglobulin lysis times were recorded by the unpublished method of Dr. Christine Hawkey, which is described as follows. To a plain glass tube 12 by 75 mm containing 2 ml 0·02% acetic acid, previously chilled to 4°C, is added 0·1 ml citrated plasma. The contents of the tube are then mixed and centrifuged at 800 *g* for four min to deposit the euglobulin precipitate. After discarding the supernatant the tube is inverted and drained on filter paper. Thereafter the precipitate is redissolved in 0·3 ml Fearnley's buffer and the solution clotted by the further addition of 0·1 ml thrombin (50 U/ml). The tube is then placed in a 37°C water-bath and observed for lysis.

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Bronchorrhoea

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Bronchorrhoea may be defined as the copious (over 100 ml daily; Keal, 1970) production of non-purulent sputum, the appearance of which suggests diluted uncooked white of egg. Bronchorrhoea replaces the older term "catarrhe-pituiteux" of Laennec. The literature on the subject is confusing and scanty, various terms are used—for example, bronchorrhoea serosa, hydromucous hypersecretion, protein bronchorrhoea, etc.—and only rarely is the phenomenon clearly defined. In the English literature there has been only limited mention of the subject.

Case Report

A 51-year-old man was admitted to hospital in June 1971 complaining of left-sided chest pain. A diagnosis of acute pericarditis was suggested and confirmed by electrocardiogram changes, enzyme studies, and the clinical course. Routine investigations including viral studies failed to define the aetiological factor. He had had no previous illness, apart from an episode of "pneumonia" during the war. Although a heavy smoker (40 cigarettes a day) he denied symptoms of chronic bronchitis and admitted only to early-morning "throat clearing." Four days after admission he developed a cough producing purulent sputum, pyrexia, and both clinical and radiological signs of bronchopneumonia. He responded satisfactorily to ampicillin, becoming apyrexial, and all radiological evidence of bronchopneumonia resolved. He continued to expectorate large amounts of non-purulent sputum, however, which had the appearance of diluted, uncooked white of egg. He was discharged home and remained well apart from two further episodes (in August and September), when the clear sputum became purulent and he developed mild dyspnoea. On each occasion there was clinical improvement after treatment with a broad-spectrum antibiotic given by his general practitioner, and the purulent sputum became clear and mucoid. Four months after the original admission he was reassessed. He was symptom-free apart from the daily production of over half a litre of clear, runny sputum. This was produced throughout the 24-hour period. Neither posture nor activity affected the volume or nature of the sputum.

Physical examination showed no abnormality apart from scattered rales and rhonchi in the chest.

Investigations in October were: E.S.R. 16 mm/hr, W.B.C. 6,500/mm³ (normal differential), eosinophils 2% (absolute count 140/mm³), electrolytes and urea normal, proteins and electrophoresis normal; 24-hour collection of sputum, 600 ml clear fluid becoming thicker on standing, no eosinophils, micro-organisms, or fungi, normal flora, no malignant cells; skin tests for type 1 sensitivity, no immediate reaction to pollens, house-dust mixture, *Dermatophagoides pteronyssinus*, furs, danders, candida, or aspergillus; chest *x*-ray picture and bronchogram normal. The results of respiratory function tests are given in the Table.

Macroscopically the saliva and sputum were similar. However, bedside examination of the sputum some 30 minutes after expectoration showed a "clot" formation. By contrast, examination of his saliva after the same time interval showed no change. Microscopically the secretions were indistinguishable. Rheological studies

Respiratory Function Tests

	Use of Bronchodilator		Predicted Value
	Before	After	
Forced expiratory volume in 1 sec (l.)	2·4	2·6	3·1
Vital capacity (l.)	3·4	3·5	4·0
Forced expiratory ratio (%)	71	74	
Peak expiratory flow rate (l./min)	440	485	455
Mixed venous P_{CO_2} (mm Hg)	41		42-50
Transfer factor (ml/min/mm Hg)	19·3		22·3
Total lung capacity (l.)	5·26		5·59
Residual volume (l.)	2·3		1·87

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