normal ovulatory cycles (Pedowitz *et al.*, 1955). The comparatively low levels obtained with the chemical method in our cases suggest that the most active oestrogens produced by granulosa-cell tumours may not appear in the urine as oestradiol, oestrone, or oestriol. Furthermore, the low level of oestrogen found in the tumours could also be explained if they are producing a potent oestrogen, not measured by Brown's techniques. It is known that there are other oestrogens in normal urine and ovaries, though their importance is usually less than the three measurable fractions (Brown *et al.*, 1959).

Estimation of urinary oestrogens may be important both diagnostically and prognostically. After removal of the tumour urinary oestrogens should return to normal levels. In both these cases there was a marked decrease in the oestrogen levels in all three fractions by the second week. In Case 2 the oestrogen level had risen again six months post-operatively.* In any event, since there has been no clinical regression in signs in either child we feel that both should have regular clinical examinations and urinary oestrogen assays. A tendency of the latter to rise further would be an indication to re-examine the remaining ovary, since bilateral tumours, though uncommon, do occur, and the second tumour may be so small as to be missed at the first laparotomy. In most cases reported in the literature, a distinct regression in pubertal signs takes place fairly rapidly after removal of the tumour in younger patients (Anderson and Sheldon, 1937; Gross, 1940; Fuller and Smith, 1941; Haines and Jackson, 1950).

We were surprised to find elevated "F.S.H." levels, since granulosa-cell tumours are presumed to be autonomous. This finding has been reported in three other cases in the literature (according to Pedowitz *et al.*, 1955). In an attempt to see if any of the oestrogen secretion was under pituitary control, we gave stilboestrol for four days, hoping thereby to suppress any pituitary over-activity. If oestrogen production was in fact under pituitary control, this should also have been depressed. The oestrogen excretion, however, was not affected. The high "F.S.H." levels would appear to indicate either that the tumours are under some pituitary control (which the above-mentioned observation does not completely exclude) or that the tumours themselves produce a substance capable of increasing the size of rat ovaries.

Summary

Three cases of precocious puberty due to granulosa-cell tumours in infancy are described, together with biochemical estimation and fractionation of both urinary and tumour oestrogen content in two of them.

It is suggested that the tumours may produce a potent oestrogen which is not measured by the current chemical methods, and may also produce a gonadotrophic substance.

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*This rise is probably not significant, since the levels are not elevated above those found in our two controls.

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ST. ANTHONY'S FIRE REKINDLED: GANGRENE DUE TO THERAPEUTIC DOSE OF ERGOTAMINE

BY

E. A. CAMERON, M.B., M.R.C.P.Ed.

AND

E. B. FRENCH, M.B., F.R.C.P.Ed., M.R.C.P.

From the Eastern General Hospital, Edinburgh

In the tenth and eleventh centuries ergot-poisoning from rye infected with *Claviceps purpurea* was a common epidemic disease in France, and was known by a number of names, such as mal des ardents, ignis sacer, and feu sacré. The emphasis on fire is explained by the violent burning pain in the limbs; sufferers unable to bear the heat in their beds sought relief in the open air. With the onset of gangrene the blackened limbs were likened to charcoal. Several houses of the Order of St. Anthony were devoted to the care of sufferers from the holy fire, and the walls of their hospitals were painted a symbolic red or flame colour. It seems beyond reasonable doubt that St. Anthony's fire originally referred to gangrenous ergotism. However, the definition of St. Anthony's fire in many dictionaries and encyclopaedias mentions erysipelas. The patient whose case is described below presented with such a remarkably red face that we felt this might have accounted for the confusion with erysipelas and other infectious skin diseases.

The literature reveals a large number of cases of ergotism in both Great Britain and America, resulting from either liquid ergot or ergotamine tartrate, despite the fact that contraindications to the use of ergotamine are well documented. They were recently summarized by Greene (1959), and include peripheral vascular disease, hypertension, and coronary disease; pregnancy; thyrotoxicosis; gross sepsis; hepatic and renal disease; and anaemia. In the *British Medical Journal* (1959), under "Notes and Comments," the expert writes: "In those persons who are sensitive its [ergotamine] use has produced nothing less than disaster. Whenever a new case is reported it becomes a matter for astonishment that responsible manufacturers make it for medical use."

That serious ergotism can occur from normally accepted therapeutic doses of ergotamine in the absence of known contraindications was forcibly impressed on us recently.

Case Report

A married woman of 45 was admitted to hospital on February 22, 1959, as a medical emergency, complaining of intense pain in the legs and arms. Her doctor had been unable to feel her radial pulses or record her blood-pressure. Thinking she had developed profound peripheral circulatory collapse, he had given her 100 mg. of hydrocortisone intramuscularly.

On examination she was fully conscious, somewhat agitated, and in severe pain. Temperature was 101° F. (38.3° C.), the face and neck were sweating and flushed to a fiery red. All four extremities were cold and mottled blue and white. Pulsation could just be felt in the femoral and subclavian arteries, but there were no pulses distal to these vessels. Blood-pressure was not recordable in any limb. The carotid pulses, however, were strikingly forceful and the aortic second sound was very loud. The heart rate and rhythm were normal and the electrocardiogram showed no abnormality. There were hyperalgesia on tendon pressure, dysaesthesia to pin-prick, but normal appreciation of light touch in all limbs. Tendon jerks were depressed in the lower but brisk in the upper limbs. The fundi were healthy. There was proteinuria (0.5 g./l.), W.B.C. 16,500/c.mm., and Hb 89% (13.34 g./100 ml.).

In view of the intense flushing of the face, bounding carotid pulses, and loud aortic second sound it was felt that the blood-pressure in the head and neck was probably high and the failure to record it in the limbs due to intense arterial spasm. The clinical features suggested the probability of ergotism.

There was nothing in her previous history to suggest any vascular disease or undue sensitivity. A week before admission she had developed mild influenza, which was then prevalent. Recently her menstrual periods had been rather erratic and a little heavier. The last one began on February 20. Further inquiry revealed that her practitioner had prescribed 1 mg. of ergotamine tartrate t.i.d. orally with a view to modifying the loss. In all, she had taken seven tablets from February 20 until her admission on the 22nd.

On February 20 she had vomited several times throughout the day and experienced considerable abdominal pain. There was no further vomiting and the pain settled. The same day, however, cramplike pains developed in both lower limbs. These persisted, and by the 22nd the forearms and hands were also affected. By then the pain was exceedingly severe in all four limbs, and her husband noticed that her feet and legs were white and very cold to touch. He applied hot-water bottles to them in an attempt to give her relief. During February 22 patchy cyanosis appeared, and because of the coldness, pain and general malaise, her doctor was recalled and he arranged her admission to hospital at once.

She had vomited after taking the first two tablets. It was the day after the drug was first taken and after consuming only two or possibly three tablets, that the legs and feet first became cold. Several of the remaining tablets were sent for assay and found to contain the stated 1-mg. quantity of ergotamine tartrate.

Management

It was anticipated that the spasm would soon wear off, and therefore only symptomatic measures for the pain were adopted, along with exposure of the limbs to room temperature and warming of the trunk. Next day, however, the ischaemia was worse. There was progressive sensory loss and the deep reflexes in the legs disappeared. The calf muscles were bunched and intensely painful. The small muscles of the hands were paralysed. Accordingly heparin was injected intramuscularly owing to the absence of accessible veins, and phenindione was given orally. Tolazoline, 50 mg., was injected into the left femoral artery just distal to the inguinal ligament. Within four minutes

there was a pronounced flushing over the upper two-thirds of the thigh extending up over the lower abdomen, but no change in the ischaemic leg and foot could be detected. The same dose of tolazoline, with 5,000 units of heparin, was injected into the right femoral artery with no better result. Intra-arterial "hydergine" (0.03 mg.) was also ineffective.

Sympathetic block, intra-arterial procaine, other vasodilators, and more active cooling of the ischaemic extremities were all considered, but were rejected for reasons given later.

The skin colour and temperature gradually improved in the upper limbs. On February 25, some 40 hours after admission, the fingers of the left hand were blue, but the rest of the hand was quite pink. The right hand was still cyanosed, and it was clear that the thenar muscles were infarcted. In the legs a line of demarcation appeared at the junction of the middle and upper thirds of the calf. By now the brachial and popliteal pulses were easily felt, and the femoral pulsation was strong. The distal pulses were still absent. Blood-pressure could now be recorded, and the first reading was 200/100 mm. Hg. By February 26 the left radial pulse had returned and there was striking improvement in the left hand overnight. Light touch could now be appreciated in the hands, excepting the right thumb and index finger. Movements in the left hand were good, though some contracture remained. On the right side, flexion contracture of fingers was present (see Fig. 1,b).

On February 27, five days from admission, the right radial pulse had returned. Pulsation of the digital arteries of the left hand and the right middle, ring, and little finger was first noticed on March 3, but may have returned earlier. Sharp lines of demarcation indicated that maximum improvement had occurred, and that amputation was advisable. The patient was transferred from the medical unit on March 7, when her general condition was good, blood-pressure had fallen to 165/100 mm. Hg, and proteinuria had disappeared. Amputation of both legs, the right thumb, and tip of the right index finger was performed. (Fig. 2 summarizes the main features of the illness.)

The blood-flow in the left hand was measured by venous occlusion plethysmography on April 22. This reached 11 ml./100 ml. of tissue/minute during indirect heating; normally it should have risen to at least 30 ml. Vasomotor control was present, since the flow fell to 2 ml./100 ml. of tissue/minute within a quarter of a minute of the application of a cold wet towel to the thighs.

An attempt was made to exclude subclinical disease such as might predispose to undue sensitivity to ergotamine. Liver-function tests were normal. Renal-function tests showed normal blood urea and intravenous pyelogram, but a reduction creatinine clearance averaging 75 l./24 hours.

FIG. 1.—(a) Five days after admission, and seven days from taking the first 1-mg. tablet of ergotamine tartrate. Maximum improvement had occurred. (b) Shows right thumb and forefinger—same time interval.