

constipation is therefore unknown to the native who is born and bred on the kraal.

Exercise is plentiful for the work though unremitting is hard and occupies all the Zulu's daylight hours. Having no easily available means of transport and not being able to afford the luxury of owning a motor car or other vehicle, he walks, and when he decides to walk distance is no deterrent.

The mental strain and worry which are such destructive forces in the civilized individual are conspicuously absent from the native's mental outlook. Whether he needs to worry or not, he apparently never does so, for his philosophy is fatalistic and his life is lived in the present. As far as he is concerned the future can look after itself. He is inclined to be happy-go-lucky and quite irresponsible being concerned chiefly with his day's work, the provision of food and a hut for his family, and the observance of his tribal customs in respect to marriage and so on. Affairs of state and high finance are not of any immediate interest to him; his life and mode of living it, is simple, healthy and, to him, full of joy.

That is the kraal dweller. But what happens to his colleague who drifts to the towns. He immediately encounters a vastly different atmosphere, different conditions, difficult situations. He comes into contact with the worst evils of civilized life, falls a prey to them, is absorbed by them and because his primitive mind is unable to grasp the significance of it all, he very soon loses control. His mode of life becomes a compromise between the kraal and the city and a tendency develops for him to acquire the diseases of civilization. Hence middle age for him also becomes more precarious than that of his country brother but never as frequently nor as markedly as in his European neighbour.

Thus briefly summarising the foregoing discussion we may conclude that:

- 1 The blood pressure in the native under the age of 35 falls well within normal limits.
- 2 Above this age there is a marked tendency towards low levels, as compared with the findings in a corresponding series of Europeans.
- 3 Hyperpiesia of an essential type is uncommon.
- 4 The influence of etiological factors explains the notable difference between the preval-

ence of high blood pressure in the middle aged native and that of the European, and also between that of the kraal dweller and of his civilized brother in the city.

- 5 Arteriosclerotic changes are likewise found to be comparatively uncommon. Here again the etiology is important.

### THE RELATION OF ERGOTAMINE AND THE OESTROGENIC PRINCIPLE TO PERIPHERAL GANGRENE.

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Ergot is derived from a fungus (*Claviceps purpurea*) which grows on rye and certain grasses and it is a variable mixture of various potent and relatively inert substances. The main active constituents are the alkaloid ergotoxine and ergotamine and the amines histamine and tyramine. According to Rothlin, the alkaloid ergotamine is the most important constituent of ergot, the one the presence of which in ergot preparations should be ensured. This alkaloid ergotamine ( $C_{33}H_{35}O_5N_5$ ) is now extensively used mainly as the tartrate, for the prevention and control of postpartum haemorrhage from atonic uteri and the treatment of retained lochia, delayed involution, bleeding following caesarean section and haemorrhage from abortion. Recently authors have advocated its use for various other conditions among which are migraine, exophthalmic goitre, pulmonary haemorrhage, pruritis, diabetes mellitus, diabetes insipidus, melancholia, prolapse of the rectum and glaucoma.

As is well known there are two forms of ergotism, the gangrenous and the convulsive. The convulsive form does not produce such highly characteristic effects as the gangrenous. It is with the gangrenous form, however, which we are concerned with here. Dale in 1906 was among the first workers in this direction and he concluded from his experiments on animals that: (1) The physiological effect of ergot preparations fall into two groups (a) Stimulant effects on plain muscular organs, prominent among which are contraction of the arteries, the uterus and the sphincter of the iris. (b) A specific paralysis of the motor elements in the structures, associated with sympathetic innervation, which

adrenalin stimulates: The inhibitor elements retaining their normal function. (2) That the two sets of effects are produced by different active principles, of which the one responsible for peripheral paralysis appears to be concerned in the central convulsant effects.

Most cases of gangrene or threatened gangrene due wholly or partly to the therapeutic use of ergotamine tartrate have occurred in women with puerperal fever. A case has been described in which a woman with severe puerperal fever, after a total dosage of .0265 Gm. of ergotamine tartrate in one week, developed excitement, formication, vomiting, diarrhoea, sweating, weak pulse, muscle contractures, fixed myosis and gangrene of the feet. Another case has been reported in which a woman with severe puerperal fever, after a total dosage of .05425 Gm. of ergotamine tartrate developed bilateral gangrene of the legs. There was thrombosis of all the veins of the amputated limbs and spasm of the arteries. Of fourteen cases of gangrene in the puerperium following miscarriage which had been attributed to ergotamine tartrate, Sainger (1929) found that in no case was there a normal labour or puerperium. Sainger also showed cases of gangrene of the extremities following the use of ergotamine tartrate for exophthalmic goitre.

From a study of the literature of the changes which occur in gangrene resulting from the administration of ergotamine tartrate the most obvious conclusion is that the vascular spasm in ergot poisoning does not arrest the circulation and so does not cause gangrene directly. The spasm profoundly slows the blood stream and leads to the secondary changes in the vessels, i.e., thrombi due to stasis from injury to the endothelium and loss of plasma.

Kaunitz, in 1930, on the basis of experiments established a definite pathological similarity between thrombo-angiitis obliterans and endemic ergotism. Not only on the basis of his experiments but also because of certain etiological resemblances, he postulated the possible implication of ergot in the causation of thrombo-angiitis obliterans. This suggestion, although definite proof is lacking, is certainly interesting and experiments are now being conducted in the Department of Medicine, where definite attempts are being made with a view to establishing this. It

has been found, that, so far there does seem to be pathologically a superficial resemblance between the two conditions.

Perusal of the literature adequately demonstrates the confusion surrounding the clinical and experimental aspects of thrombo-angiitis obliterans. The knowledge that one has concerning this malady has been gleaned from purely clinical and statistical research. Experimental investigation has been directed almost exclusively toward establishing a specific bacterial etiological agent for the disease, and has thus far failed completely or the results have been so meagre as to be altogether inconclusive. With regard to the pathology of the condition, there is no unanimity of opinion among the students of the disease. Buerger, in his description of the pathogenicity postulated the following series of events: There is an initial acute inflammation with polymorphonuclear leucocytic infiltration of the perivascular tissues and of all the coats of the vessels. Synchronously, thrombosis occurs in the area of inflammation. This is followed by replacement of the inflammatory cells by connective tissue, organisation and canalisation of the thrombus and finally a great overgrowth of connective tissue in and about the adventitia, binding the artery, the vein and the nerve together.

Whether or not there is such an etiological relationship between ergot and thrombo-angiitis obliterans as Kaunitz suggested it is difficult to say. Nevertheless, it is felt that one may reasonably accept ergot arteritis and ergot gangrene as a typical pathological process on which to base further studies. The results while not directly translatable in terms of thrombo-angiitis obliterans, at least suggest possibilities in the ultimate solution of the problem.

It has been found that just as the male has been the more predominant victim in Buerger's disease, so the male is the more predominant victim in epidemics of gangrenous ergot poisoning. Also, it has been demonstrated, that the predominant histo-pathological features of gangrenous tails of ergot poisoned rats is marked cellular proliferation and swelling of the intima especially in the smaller arteries and arterioles. This is also the case in Buerger's disease.

From the experiments conducted in this department, it was possible to demonstrate that although gangrene could be produced in both

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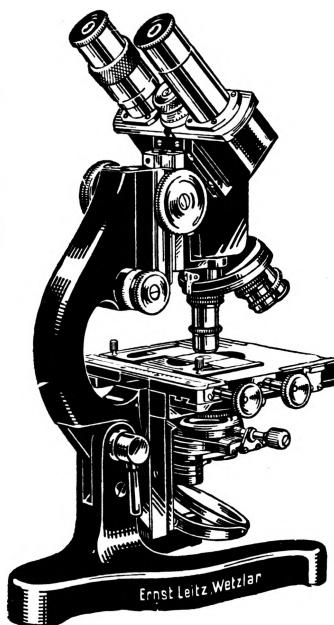
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males and females, the females could be completely protected by the use of sufficiently large daily doses of oestroform, while the males were incompletely protected. The conclusions drawn from these experiments is that in the case of both ergot poisoning and of thrombo-angeitis obliterans the female may be protected by a sex hormone, probably the oestrogenic substance of the ovary.

Further details of the experiments conducted show that in the rat, after an injection of ergotamine tartrate in dosages varying from 25 to 100 mgm. per kilogram of body weight, pallor of the tail occurred after three to five days, cyanosis and exquisite pain in from six to nine days, blackening in from ten to sixteen days and demarcation in from seventeen to twenty days. This was followed by sloughing of the gangrenous portion. The injection of oestroform following the administration of ergotamine tartrate was able to prevent the development of gangrene in female rats but not in male rats, but the male rats which developed gangrene did not obtain it to such a marked extent as the control rats.

Pathologically there was a marked cellular proliferation and swelling of the intima, which was the most evident in the smaller arteries and the arterioles. In some sections the lumen was almost completely occluded.

As a side experiment, injections of large amounts of ergotamine tartrate into rats over a long period showed no change at all in the coronary arteries. This experiment was performed because of the greater occurrence of coronary thrombosis in the male than in the female.

From the conclusions arrived at in the above experiment and from a study of the literature it seems that the oestrogenic principle seems to be a definite factor in peripheral gangrene. This is supported by the following facts:—

(1) Of twenty cases of Buerger's disease reported in female subjects, six were operated on previously for removal of ovaries three to seven years before the occurrence of Buerger's disease; of the remaining fourteen all incurred the disease after the menopause.

(2) Peripheral gangrene resulting from the use of ergotamine tartrate during labour or in the puerperium occurs more commonly where there is difficulty in labour or some disorder to their assistance at their call without of pregnancy or where there is puerperal sepsis.

Recent literature suggests that the female sex hormone has a great deal to do with labour and pregnancy. It would thus seem that the peripheral gangrene and the deficiency of oestrogenic principle are related to each other.

(3) The occurrence of peripheral gangrene in cases of exophthalmic goitre which were treated with ergotamine tartrate. It is well known that the thyroid and the pituitary glands have a definite influence on each other, and that the pituitary by means of the secretion from the anterior lobe has a profound influence on the secretions from the ovary. This disturbance of the hormonal secretion, which may take place in diseases of the thyroid and the pituitary may predispose the patient to peripheral gangrene when ergotamine tartrate is used therapeutically in the disease.

It may thus be concluded, that the peripheral gangrene from the use of ergotamine tartrate is not due directly to the ergot itself, nor is it due to the vascular spasm as a result of the ergot, but possibly to the circulation of some toxin, or the deficiency of some substance, probably the oestrogenic principle, in the vessels and in the tissues, and the ergot preparations merely act as a sensitising factor in the production of the peripheral vascular stasis.

It is hoped that this work showing the relationship between the oestrogenic principle and peripheral gangrene due to the use of ergot preparations may have its genesis in an effort to open a new avenue of approach to the problem of thrombo-angeitis obliterans.

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The physician is one who, esteeming all the wretched as equals, as all men are equals in the eyes of the Divine Being, eagerly hastens there is difficulty in labour or some disorder to their assistance at their call without of pregnancy or where there is puerperal sepsis. distinction of persons—*Hippocrates*.