appear that fewer good results were obtained during months 1 + 2 than during months 3 + 4; this is more apparent in Table III. The difference is not significant ($\chi^2=1.302$); nevertheless it seems possible that the suggestibility of the patients may have been heightened towards the latter part of the trial, so that those who had not yet experienced relief from the treatments they had had so far presumably thought that some of the later treatments ought to be effective.

Table IV sets out the results of the different treatments, irrespective of months. It will be seen that complete relief of symptoms occurred most often with mephenesin, but that when the "very good" and "good" results combined were compared with the poor results, there was not much to choose between mephenesin, ethisterone, or mephenesin + ethisterone. The placebo, though less effective than the above, was by no means devoid of apparent value.

Tables V and VI compare mephenesin with the rest and ethisterone with the rest. The similarity in these groups of figures will be noticed. None of these differences is statistically significant.

Discussion

The results of this limited trial suggest that both ethisterone and mephenesin have some value in the treatment of the premenstrual syndrome, but that neither can be expected to help more than about 60% of patients. The combination of mephenesin and ethisterone appears to be no better than either substance alone. Mephenesin alone completely relieved eight patients, whereas ethisterone and ethisterone + mephenesin had this effect on only three each, and the placebo did as well in two patients. Table I shows that of the 21 patients who had all four treatments, only 3 had no relief from any treatment, 10 benefited from either ethisterone or mephenesin, and 8 appeared to be helped by both.

The incidence of side-effects was notably low both with mephenesin and with ethisterone; in point of fact, more complaints of these were recorded for the placebo than for the other tablets.

Since in this trial either ethisterone or mephenesin alone helped some 60% of patients, and one or the other was of some value to about 90% of the patients, it is apparent that hormonal imbalance may not be the sole cause of the symptoms in at least some of the patients. The evidence suggests that psychological factors, manifesting themselves in tension states, may be an important part of the premenstrual syndrome in some cases, and where successful treatment does not follow from ethisterone therapy the use of mephenesin might well be considered.

Summary

A clinical trial of ethisterone and of mephenesin, alone and in combination, for the treatment of premenstrual symptoms has been carried out by means of a random block design, whereby the effects of the various treatments could be compared with each other and with those due to a placebo.

While mephenesin produced complete relief more often than ethisterone, an overall analysis suggests that there is little to choose between them. Either substance alone helped only some 60% of patients, and a combination of the two was no more effective; but one or the other was of some value to about 90% of the patients.

My thanks are due to Dr. Mary Parkes for referring the majority of the patients to me for the purposes of this trial; and to Dr. B. M. Merriman, of British Drug Houses Ltd., for supplying the sets of tablets.

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ANTERIOR TIBIAL SYNDROME FOLLOWING ARTERIAL EMBOLISM

BY

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Carter *et al.* (1949) described a syndrome consisting of ischaemic necrosis of the muscles of the anterior tibial compartment of the leg, with a lesion of the anterior tibial nerve. Their 10 patients were fit young men, in eight of whom the onset was clearly related to strenuous unaccustomed exercise involving the use of the leg muscles. The condition developed in their two remaining cases after transfusion into the affected limb. The main clinical features were pain, swelling, redness, and tenderness in the front of the leg. There was inability to dorsiflex the foot and toes. The peroneal muscles were not affected. Involvement of the anterior tibial nerve produced paralysis of the extensor digitorum brevis muscle and sensory loss on the dorsum of the foot. The degree of residual foot-drop was lessened by the development of contracture in the affected muscles.

Vogt (1943) described the first similar case. Sirbu *et al.* (1944) described one case in which both legs were affected after marching, and another which followed repair of a small muscle hernia through the anterior crural fascia. Horn (1945) reported two cases in young soldiers after marching, and Phalen (1948) described the case of a young man who developed the syndrome after walking half a mile. The case of a young Greek who showed the same condition in both legs after long-jumping on a concrete pavement was recorded by Pearson *et al.* (1948). Hughes (1948) described three cases of "ischaemic necrosis of the anterior tibial muscles due to fatigue." Two were in healthy men who played football before the onset of their symptoms, and the third case occurred in a young man suffering from a febrile systemic illness, possibly polyarteritis nodosa. Tillotson and Coventry (1950) described a case in a hiker following his first walk of the season. Horn and Sevvitt (1951) reported a case in which the syndrome was included in the sequelae of a traumatic rupture of the popliteal artery. Similar symptoms were noted by Psaki and Schields (1952) in a soldier who sustained a twisted ankle.

Below, two cases are described in which the syndrome followed arterial embolism.

Case 1

A woman aged 51, who had chronic rheumatic heart disease, with aortic incompetence, mitral stenosis, and controlled auricular fibrillation, was admitted to hospital on May 25, 1954. There was a moderate degree of peripheral arteriosclerosis. She complained of severe pain, of sudden onset, in the right calf. The right lower limb was found to be cold and pale up to a handbreadth below the knee; the toes were deeply cyanosed, and gangrene appeared likely. The right popliteal pulsation was much weaker than the left and no pulsations could be felt at the right ankle. The right femoral pulsation and all pulses in the left lower limb were normal. A diagnosis of arterial embolism was made and treatment begun with analgesics and oral vasodilators (nicotinic acid, 100 mg., and tolazoline hydrochloride, 25 mg., both thrice daily). The affected leg was exposed and the foot supported in a right-angled splint.

On May 26 she complained of severe pain in the front of the right leg, and this region was seen to be swollen. The maximum calf circumferences were right 12 in. (30 cm.) and left 10½ in. (26.5 cm.), but measurements from the fibulae posteriorly round to the anterior tibial borders were equal. The swollen area was bright red in colour, fading a little in the lower third of the leg, and very tender. The patient was unable to dorsiflex the foot and toes. Voluntary movement was present in the peroneal and posterior tibial muscle groups but was limited by pain. The right ankle-jerk, which had previously been normal, was now diminished. Sensation to light touch and to pinprick was reduced in the lower part of the leg and was absent over the toes and dorsum of the foot.

Over the next three weeks the condition of the right leg slowly improved, though pain remained troublesome. The toes became normal in appearance and the temperature of the leg and foot increased slightly. A weak right posterior tibial pulse became palpable. The redness and tenderness diminished, becoming more localized in the upper third of the leg. There was some reduction in the swelling of the anterior tibial compartment, but dorsiflexion of the foot and toes remained impossible. Sensation returned to the lower part of the right leg and foot, though not to a small area on the dorsum of the foot proximal to the first interdigital cleft.

On June 16 the patient suddenly became unconscious and died after ten minutes. It was thought that a cerebral embolus was responsible, but permission for necropsy was not obtained.

Case 2

A woman aged 70, who suffered from mild hypertension and auricular fibrillation, was admitted to hospital on November 10, 1953. She gave a history of sudden onset of severe pain in the left calf, beginning seven hours before admission. Examination showed considerable peripheral arteriosclerosis. The left lower limb was cold and pale from the knee downwards and the popliteal and ankle pulses were absent. The left femoral pulsation and all pulses in the right lower limb were present and normal. The patient was unable to dorsiflex the foot and toes. The peroneal and posterior tibial muscles showed slight weakness. The left ankle-jerk was reduced and all forms of sensation were diminished below the left knee. A diagnosis of arterial embolism was made. Treatment consisted of analgesics, elevation of the head of the bed, and exposure of the affected limb. The foot was supported in a right-angled splint. Tolazoline hydrochloride was given orally—50 mg. thrice daily. Papaverine sulphate (60 mg.) was given by intra-arterial injection (Edwards *et al.*, 1952). Paravertebral lumbar sympathetic block was performed (Dr. G. Jackson Rees) on November 11 and 12.

On November 13 the patient complained of pain in the front of the left leg. Examination showed redness of the skin over the anterior tibial compartment with some swelling and acute tenderness. The redness gradually faded over the next three weeks, as did the tenderness. The swelling subsided in about six weeks and the anterior tibial muscles then felt woody. During this period the left leg and foot became warmer. The peronei and posterior tibial muscles regained normal power, but there was no recovery of dorsiflexion of the foot and toes. Sensation to light touch and to pinprick returned to the leg and foot.

By January 8, 1954, she was able to walk. Although passive plantar flexion of the left foot was partly limited by contracture of the anterior tibial muscles, the degree of foot-drop required a toe-raising spring. Domestic circumstances delayed her discharge from hospital until April 9. At this time the anterior tibial muscles still felt woody and showed no wasting. A weak left dorsalis pedis pulsation had become palpable, though the left foot remained colder than the right. She did not attend for follow-up, and inquiries revealed that she died at home on May 26, the cause of death being a cerebral vascular accident.

Discussion

Although these cases occurred in older patients, and although the main clinical features did not appear for two to three days after the embolism, they conform to the description of the anterior tibial syndrome. This syndrome has not previously been described following arterial embolism. Haimovici (1950) does not include it in a review of peripheral arterial embolism and its sequelae. Mufson (1952), discussing the neurological complications of peripheral vascular disease, does not mention the condition.

Two main views have been put forward to explain the production of ischaemic necrosis of the muscles of the anterior tibial compartment. The walls of the compartment do not allow of rapid distension, and Carter *et al.* (1949) suggested that a raised pressure within the compartment, produced either by the muscle trauma of unaccustomed exertion or by leakage of transfused fluid along the tendon sheaths, was the main causative factor and operated by reducing the blood supply to the affected muscles. Hughes (1948, 1949) considered that the syndrome had a primarily vascular basis and showed that the histological changes were similar to those found in Volkmann's ischaemia. He pointed out that an increased tension in the compartment should affect all muscles equally. There was in fact a varying incidence of damage to the three muscles in the anterior tibial compartment, and he suggested that this variation might be related to differences in their blood supplies. He concluded that segmental spasm of the anterior tibial artery was responsible for the syndrome.

The two present cases lend support to the view that the anterior tibial syndrome has its origin in vascular inadequacy. Profound arterial spasm is a well-recognized concomitant of embolic arterial occlusion. The appearance of the syndrome after an interval of two to three days may have been due to a delayed improvement, either spontaneously or as a result of treatment, in the blood supply to the leg muscles. This would cause swelling of the muscles, and in the anterior tibial compartment increased tension might well lead to further interference with blood supply. The cases described by Carter *et al.* (1949) following exertion or transfusion did not show any significant impairment of peripheral blood flow in the limbs affected, but the shortest interval between symptoms and examination was one week in nine of their ten cases. It seems possible that spasm of the anterior tibial artery may have occurred in these cases, passing off before the development of the syndrome. This explanation must remain hypothetical until similar cases are studied at the earliest stage.

Carter *et al.* (1949) differentiated the anterior tibial syndrome from cellulitis of the leg, osteomyelitis of the tibia, tenosynovitis, acute thrombophlebitis, and traction lesions of the lateral popliteal nerve. Ferguson and Liversedge (1954) described nine cases of ischaemic lateral popliteal nerve palsy. These cases differed in certain important respects from the anterior tibial syndrome (involvement of the peroneal group, muscle wasting, and electromyographic findings), though three cases appear to have followed acute arterial occlusion, and one developed after a transfusion and another after an injection, into the saphenous vein.

In discussing treatment of those cases of the syndrome which followed undue exertion involving the legs, Carter *et al.* (1949) advised graduated training as a prophylactic measure. For the acute stage they suggested complete rest of the affected limb, and, if improvement did not occur, surgical decompression of the anterior tibial compartment by fasciotomy. The necrotic muscles are, however, prone to infection (Hughes, 1948). Decompression was considered in the two cases now described but not employed, as it was felt that the onset of gangrene might thereby be hastened. Psaki and Shields (1952) described improvement in muscle power following lumbar sympathectomy as late as eleven months after the first symptoms. If spasm of or obstruction to the anterior tibial artery is indeed a causative factor, measures

designed to relieve vasospasm or to promote vasodilatation will be valuable, particularly at an early stage. When there is clinical evidence of raised tension in the anterior tibial compartment surgical decompression would seem to be reasonable, if by so doing survival of the limb is not prejudiced.

Summary

Two cases in which the clinical features of the anterior tibial syndrome followed arterial embolism are described. Pathogenesis, diagnosis, and treatment are briefly discussed.

I am indebted to Dr. E. T. Baker-Bates (Case 1) and to Dr. C. S. McKendrick (Case 2) for permission to report these cases.

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THE ROLE OF SULPHONAMIDES IN THE INFECTIVE DIARRHOEAS OF AFRICAN CHILDREN

BY

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The problem of diarrhoea in infancy and childhood has been the subject of much research; owing to the multiplicity of causes a very careful clinical, bacteriological, and biochemical assessment may be required before an accurate diagnosis can be made and effective treatment selected.

In many tropical and backward countries immediate laboratory services are not always available, medical personnel is limited, and clinical examination alone may fail to reveal the presence of more than one disease. The discovery of otitis media or pneumonia in a child presenting with diarrhoea does not preclude the fact that there may be a coexisting bacillary dysentery even in the absence of blood and mucus in the stools.

The problem of selecting treatment is equally complex if one is to provide a satisfactory standard of therapy within the economic limits of a rapidly developing community.

In infantile gastro-enteritis in which no pathogenic organisms are isolated from the stools, sulphonamides are considered to be of doubtful value, and a regime of graduated feeding and parenteral fluids (with or without the more recent antibiotics) still forms the basis of treatment. In bacillary dysentery sulphonamides are widely used and the "non-absorbable" compounds have been accepted as the standard treatment in many countries.

Present Investigation

The original object of the present experiment had been to assess the efficacy of the "absorbable" sulphonamide sulphadimidine ("sulphamezathine"), as compared with the "non-absorbable" compounds, sulphaguanidine and phthalylsulphathiazole ("thalazole"), in the treatment of bacil-

lary dysentery in children. As it proved impracticable to await the result of a stool culture before beginning treatment, it was decided that all cases presenting with diarrhoea as their main symptom should be included in the trial.

Although the scope of the trial was thus widened to include many possible diseases and the scientific limitations were fully realized, it was hoped that the results might be of some value to others in assessing the efficacy of sulphonamides in the treatment of infantile dysentery and non-dysenteric diarrhoea, and establishing, if possible, the drug of choice.

Sulphaguanidine has become well established in the treatment of bacillary dysentery and is recommended as the most suitable drug in tropical countries because there is little or no danger of crystalluria, and it has the advantage of rarely causing unfavourable side-effects (Boyd, 1951; Scadding, 1944). It is considered most effective in the early stages of an acute attack, but of least value when treatment is started late in the illness (Lyon, 1943; Brewer, 1943). This is of considerable practical importance in communities who do not seek medical advice until local remedies have failed and the disease is in an advanced or chronic stage. A further disadvantage so far as children are concerned is the high dosage of sulphaguanidine which is recommended. In an acutely ill and dehydrated child there is often difficulty in ensuring that the appropriate dose is swallowed.

Poth and Ross (1944) claim that phthalylsulphathiazole is highly specific in Flexner dysentery and have also proved it of value in the treatment of non-dysenteric diarrhoea. This, however, has not been borne out by Brodie *et al.* (1946), who found that it took longer to effect a cure with phthalylsulphathiazole than with either sulphaguanidine or controls, but that it reduced considerably the number of bacteriologically positive cases during convalescence. Both sulphaguanidine and phthalylsulphathiazole have the disadvantage of failing to control a parenteral or secondary infection which may complicate or perpetuate the state of diarrhoea.

Since it is known that the dysentery organisms inhabit the mucous membrane lining of the intestinal tract, the "absorbable" sulphonamides have the advantage of reaching the source of infection both through the lumen of the gut and via the blood stream (Hardy and Watt, 1944).

From previous experiments (Hardy, 1945) sulphadiazine has been recommended as the sulphonamide of choice in bacillary dysentery, with sulphadimidine of almost equal efficacy. Watt and Cummins (1945), however, place sulphadimidine in the undesirable class of sulphonamide owing to the greater percentage of toxic reactions observed in their series.

Although the possibility of renal complications with "absorbable" sulphonamides must always be borne in mind, particularly in hot climates, sulphadimidine is reported to be more highly soluble in all urines than sulphadiazine (M.R.C., 1945), and was therefore chosen for use in the present trial.

Realizing, therefore, the various advantages and disadvantages of the drugs employed, the experiment was designed as follows:

Selection of Cases.—All infants and children entering the medical wards of King George VI Hospital, Nairobi, with the main presenting symptom of diarrhoea, were admitted to the series and each succeeding case was treated with phthalylsulphathiazole, sulphadimidine, and sulphaguanidine respectively.

Clinical Assessment.—The severity of each case on admission was classified as follows: mild, moderate, severe, or moribund. As it was rarely possible to obtain an accurate history from the parents regarding the length of illness and the number or character of the stools passed daily, the clinical assessment was made on the general appearance, toxicity, and hydration of the patient. This assessment and the subsequent daily records of progress were made personally to ensure uniformity throughout the series. The groin temperature was recorded twice daily.