Discussion

The results of these first field trials indicate that the compound 377 C 54 has an appreciable schizontocidal action on *P. falciparum*, *P. malariae*, and *P. ovale* infections.

Of the *P. falciparum* infections cleared by 100 mg. of 377 C 54, the speed of clearance did not differ statistically from that for chloroquine. But at the higher single doses of 200 and 300 mg. respectively the clearance times for the new drug was significantly faster ($P < 0.001$) than that for chloroquine at 100 mg. This is of particular interest, since in a previous field trial the clearance times for single-dose chloroquine at 100, 200, and 300 mg. respectively did not differ significantly one from another (Charles and Bruce-Chwatt, unpublished).

Judging by the comparative clearance rate with single doses of the new drug and of chloroquine it appears that 377 C 54 is approximately one-half to one-third as active on *P. falciparum* as chloroquine. This is reasonably consistent with the experimental findings of the activity of 377 C 54 against *P. gallinaceum*.

The fact that at week 4 there was no evidence of a significant decrease of the spleen rate or of the average enlarged spleen in any of the six dosage groups of 377 C 54 suggests that the action of the drug is not as complete as that of 4-aminoquinolines given at single doses of 200 or 300 mg. (Charles, in print). Apart from the single doses of 100 mg. and 200 mg. of 377 C 54 which did not completely clear the parasitaemia in the respective groups, the clearance time for the other dosages was directly proportional to the amount of the drug administered. The steepness of the dose response curve on human malaria parasites is of interest and in accordance with experimental findings in *P. gallinaceum*. The rate of reappearance of parasitaemia indicates that 377 C 54 is a quick-acting and rapidly excreted antimalarial.

Summary

The results of the first field trial on African children of 377 C 54, a new antimalarial compound belonging to a series of mono- and di-hydroxynaphthalenes, indicate that the drug has a pronounced schizontocidal effect on *P. falciparum*, *P. malariae*, and *P. ovale*. There is no evidence of any direct gametocytocidal or sporontocidal action on *P. falciparum*. The new compound is well tolerated in a dosage of about 30 mg. per kg. given in two days.

We are grateful to Sir Samuel Manuwa, Chief Medical Adviser to the Federation of Nigeria, for permission to publish this paper; and to Dr. R. S. F. Hennessey, Director of the Wellcome Laboratories of Tropical Medicine, London, for supplying the new compound and for his valuable suggestions.

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Which Way Now? is a leaflet issued by the National Association for Mental Health for parents of mentally handicapped children. The leaflet describes how such children, for whom ordinary schools are unsuitable, are placed under "supervision" by a mental welfare officer or a health visitor, who will help and advise the parents as necessary. Occupation centres, which are similar to special schools, may be provided by the local health authority. If there is no occupation centre the health authority may employ a "home teacher" at regular intervals. This leaflet (price 3d. net), and others also concerned with the training of mentally handicapped children, are obtainable from the National Association for Mental Health, 39, Queen Anne Street, London, W.1.

ANTIVENENE REACTION FOLLOWING ACCIDENTAL SEA-SNAKE BITE

BY

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The following personal experience illustrates some problems in snake-bite and its treatment.

Case Report

On September 23, 1955, sea-snakes were being manipulated to obtain venom. At that time the technique used was to grasp the neck of the sea-snake with a long pair of forceps and lift it from the glass bowl in which the snakes swam. The snake was then laid on a table and seized by the left thumb and index finger either between the head and forceps or just behind the forceps (depending on how near the forceps were to the head). The forceps were then released and venom was taken on a plastic spoon. An adult *Enhydrina schistosa* (Daud)—total length 810 mm. (32 in.)—was being held thus by forceps on the table, but as my finger approached to grasp the snake, it managed to turn its head quickly (with far greater speed than I thought possible in this usually sluggish species) and bite the tip of my finger. This was at 2.50 p.m.

The snake was rapidly returned to its bowl and the index finger, bleeding slightly, sucked with much dismay. Amputation was considered, but the means were not immediately to hand. It was therefore decided to "take a chance." At the same time, I thought that if the chance did not come off, inactivity would not appear—even posthumously—to have been masterly. Without faith in the procedure, antivenene therapy was therefore given as follows: 3.10 p.m., 250 mg. of cortisone by intramuscular injection; 3.20 p.m., 10 ml. of antivenene intramuscularly; 3.25 p.m., a further 10 ml. of antivenene together with 1,000 units of hyaluronidase intramuscularly. The antivenene was polyspecific against *Naja naja*, *Bungarus coerulesus*, *Vipera russelli*, and *Echis carinatus* and concentrated by sulphate. It has negligible *in vitro* neutralizing power against *E. schistosa* venom (Savoor, 1955).

Until 6 p.m. there were no symptoms suggesting sea-snake poisoning. The bite mark was painless and there was no objective sensory loss over the index finger. Neurological and general physical examinations were negative. Routine venom-taking was resumed, the *E. schistosa* specimen which bit me giving an unusually high yield (after drying, it weighed 27 mg.; the average maximum for this species is 15 mg.). At 6 p.m. generalized aches, stiffness, and some muscular weakness started. Sleep that night was disturbed, but no further symptoms of sea-snake poisoning developed. The next morning the stiffness was much better although still present. Both palms were red and swollen. On September 25 and 26 I felt quite well but had a pricking sensation at the site of the bite. X-ray examination showed an opacity in the finger pulp. With the help of a dissecting microscope I extracted a grooved fang.

On September 27 urticaria started, the next day general aches, and on September 29 lip-swelling and conjunctival congestion developed. Promethazine, 50 mg. twice daily, temporarily relieved these symptoms, but malaise remained severe. At 6 p.m. on September 30 the neck was stiff and painful. At 9 p.m. twinges were passing down both arms. At 1 a.m. on October 1, I was woken by violent shooting pains down the arms and over the left buttock: they were agonizing and were not significantly relieved by 100 mg. of promethazine and 8 tablets of aspirin. Further sleep was impossible. Throughout that day severe pains continued despite 8 codeine compound tablets and 100 mg. of pethidine. Nausea was constant.

On October 2 root pains had diminished, but pain and, later, moderate swelling of the joints of both ankles, knees, elbows, and wrists, and of the fingers started. A scarlatiniform rash appeared over the trunk and limbs. There were fever, general weakness, and exhaustion. At 10.30 a.m. 200 mg. of cortisone was taken orally, and by 1 p.m. all pains had disappeared. The relief was dramatic. At 4.30 p.m. ankle-joint pains recurred and 100 mg. of cortisone was taken. Weakness in the left arm was first noticed. At 8.30 p.m. there was no pain, but I was now quite unable to lift the left arm. A papulo-vesicular rash had appeared round the knees.

On October 3 I felt much better and resumed work. The legs ached on standing and there was inability to abduct the left arm and difficulty in lifting the right arm. Oral cortisone, 25 mg. thrice daily, was continued. On October 5 general aches and root pains recurred. Prednisolone, 20 mg. daily, was substituted for the cortisone, but weakness and aching pains increased. The latter were constant in the left shoulder and upper arm, with exacerbations there, in the buttocks, and sometimes in the right arm. Momentary acute jags, like adhesive plaster being torn off the skin, occurred in various sites. These symptoms continued more or less unchanged during the next two weeks. They were always worse at night and were eased by codeine tablets. After October 13 prednisolone was reduced as it did not seem to be of much benefit, and was stopped on October 17. By October 26 the pains were less severe and the strength of the left arm and shoulder had improved so that the hand could now be used to brush the hair. Power in the right arm seemed almost normal.

On November 3 the remaining symptoms were an aching pain on sustained elevation of both arms, more severe on the left, occasional paraesthesiae across the shoulders and right knee, and stiffness of the right ankle. A visiting neurosurgeon found weakness and wasting of the left deltoid, infraspinatus, biceps, and (slightly) triceps. The tendon reflexes of the left arm were depressed. There was altered sensation over the left fifth cervical and right third lumbar dermatomes. During the following year these symptoms gradually diminished, and in August, 1956, an objective neurological examination was essentially negative. Prior to the antivenene, no horse serum had been injected. Previous and family histories were not relevant.

Discussion

Personal experience of the ailments we try to treat is often revealing. The literature on snake-bite contains few accounts by medical victims. Day (1869) described being bitten by *E. schistosa* whilst wading off the Orissa coast. The snake bit his heel so tenaciously it had to be shaken off, leaving two clear fang marks, but no symptoms of poisoning followed. Haast recovered from a bite by *B. coeruleus*, after neurotoxic symptoms (Haast and Winer, 1955). During the preceding five years he had been inoculated with *Naja* venoms—but these antigens would not raise his immunity to *Bungarus* poisoning. Herpetologists are not infrequently bitten (Minton, 1950; Benn, 1951; Watt *et al.*, 1956). Carelessness is usually the main factor in such accidents, sometimes even bravado (Forné, 1888; Tidswell, 1906). As a result of being bitten, my technique was modified (Reid, 1956).

The symptoms from September 27 onwards were typical of a serum reaction and were not related to the venom. Poisoning due to the venom was limited to stiffness and weakness starting three hours after the bite and lasting 24 hours. The triviality of these symptoms is remarkable when one considers that an hour after biting me the specimen yielded 27 mg. of venom, the equivalent of about 14 lethal doses for an adult (Reid 1956). It is true that my finger was pulled away swiftly, but, if there was time for a fang to be left behind, this should be sufficient for the injection of 2–3 mg. of venom. Taking venom from different species of sea-snakes, I have often seen it deposited instantaneously. This experi-

ence supports my belief (Reid, 1956) that venom ejection is primarily dependent on instantaneous secretion rather than a syringe-like expulsion of what happens to be "in store."

Snake-biting of mankind is a defensive act; the stimulus to reflex secretion is weak and rarely results in a "business bite." Otherwise it is difficult to understand why the mortality from bites of poisonous snakes should be so low considering their potential lethality. For example, M'Kenzie (1820) reported 15 sea-snake bites without a death. In a recent survey of fishing villages, several fishermen recounted to me bites in which, as in the case of Day (1869), the sea-snake stuck like a limpet yet few symptoms of poisoning followed. Only slight poisoning was observed by Lamb (1904) in 8 out of 11 patients bitten by identified *N. naja*. Martin (1907) recorded the case of a snake-charmer who was bitten on many occasions by *Notechis scutatus* (the most poisonous land snake in the world). Ferguson (1926) reported that out of 88 patients bitten by Australian neurotoxic snakes 23 victims had no symptoms of poisoning whatsoever. Jutzy *et al.* (1953) reported 55 cases of snake-bite in the Panama Canal zone, and 32 of these had no evidence of poisoning. In six of the latter the snake was identified as poisonous. One of their fatal cases was a herpetologist who had been bitten on some 20 previous occasions. Watt *et al.* (1956) reported the case of a herpetologist bitten on 10 occasions by American pit vipers: in six of these incidents symptoms were minimal.

First-aid Measures

Absorption of venom is rapid. Active first-aid measures short of immediate radical excision or amputation are ineffective (Reid, 1956). It is interesting to contrast theory—for some time prior to being bitten I had been critically considering the problem of first aid in snake-bite—with personal practice. I did nothing. The outcome may well have been due to luck, but, regardless of whether customary first-aid measures are effective or not, my point here is, are they practical?

If effective antivenene is available the sooner it is given the more likely will it help the patient. It was therefore of great interest to note afterwards how long it took before antivenene was given. Although the bite occurred in hospital, where a "snake-bite treatment box" with polyspecific antivenene, cortisone, adrenaline, and sterile syringes is immediately available in the hospital dispensary, antivenene injection was not completed until 35 minutes after the bite. This made me wonder what the delay was with ordinary patients. It emphasized how essential it is that patients coming to hospital with snake-bite should be regarded as medical emergencies.

Doubts of Efficacy of Antivenene

Grave doubts have recently been expressed regarding the practical efficacy of "neurotoxic" antivenene at present available (Reid, 1956). In many hospitals (probably most) antivenene is given to all victims of snake-bite even when there is no evidence of poisoning or the patient was bitten so long ago that no benefit would result. Sometimes the antivenene given is virtually useless for the particular varieties of snake-bite in the area concerned. It is therefore important to consider the harm antivenene may do. Serum reactions are commonly of two types—anaphylaxis, which occurs immediately (if within a few minutes it may be fatal), and serum sickness, which starts later, usually 7–10 days after the injection. Records of anaphylaxis attributed to antivenene are not common, but many accounts of snake-bite describe symptoms highly suggestive of such reactions. For example, Efrati and Reif (1953) reported 65 cases of viper bite in Israel with a high proportion of allergic symptoms ascribed to the venom. Shannon (1953) remarks that such symptoms are often regarded as due to the venom when they are in reality due to the antivenene.

Whilst hypersensitivity to snake venom may well occur, it is significant that the patient reported by Watt *et al.* (1956)

showed no signs of it despite repeated bites from each of three species of pit vipers. Faraker (1924) described a near-fatal reaction starting whilst refilling the syringe for the second half of antivenene. In this case, even the diagnosis of snake-bite was doubtful. Jörg (1935) recounted the case of a patient dying from pulmonary oedema 15 minutes after 20 ml. of antivenene injected intravenously. Flecker (1952) reported a case needing adrenaline and promethazine, which did not entirely prevent reactions. Grasset and Christensen (1947) recorded that serum reactions with South African antivenene were not rare even though the antivenene was concentrated by sodium sulphate. Minton (1952) has seen several severe reactions probably more dangerous and unpleasant than the snake-bite. Shannon (1953) mentions "several authenticated fatalities." The incidence of antivenene anaphylaxis in U.S.A. must be greatly diminished by the custom there of using the subcutaneous route.

In Penang General Hospital intravenous injection of 20 ml. of antivenene used to be a routine procedure. Anaphylactic reactions occurred more often than not. Some were so severe that doctors in the out-patient department became afraid of snake-bite cases mainly because they would have to give antivenene. These reactions became exceptional when combination with hyaluronidase and change to the intramuscular route were adopted. But were fewer antivenene reactions accompanied by a corresponding loss of therapeutic effect? The incidence and severity of anaphylaxis are directly proportional to the speed and quantity with which the antigen serum reaches its "target." Almost certainly the therapeutic efficacy bears the same relation. One is faced with the Scylla of anaphylaxis and the Charybdis of delay nullifying benefit to the patient. Two outstanding clinical problems are the indications for antivenene in snake-bite and effective dosage in relation to the time elapsed since the bite with snake-poisoning.

Serum Sickness

There are few records of late serum reactions following antivenene. Reid and Flecker (1950) described mild serum sickness seven days after *N. scutatus* antivenene. Miller and Stanton (1954) reviewed the literature of neurological complications of serum treatment without mentioning antivenene as a possible cause. Pacheco e Silva (1933) reported a case of serum sickness following scorpion antivenene. The patient had radiculitis almost identical to mine. I have been unable to find a previous record of neuropathic serum sickness due to snake antivenene. Miller and Stanton remark that "the patient is rarely treated for the complication by the physician who gave the original injection: the relation between inoculation and subsequent neurological symptoms may pass quite unrecognized." This would apply to serum sickness generally, and many instances following snake-bite may be overlooked. Swaroop and Grab (1954) estimated that about half a million people in the world were bitten each year by snakes. According to Laurent and Parish (1952), the incidence of serum anaphylaxis may not have been appreciably reduced by modern processing, whereas serum sickness has fallen from 40-60% of injections with crude serum to 20-30% with ammonium and sodium sulphate concentration and to 5% with enzyme refining.

If a quarter of a million victims are given antivenene each year, the incidence of serum sickness might well be 100,000, as few antivenenes are enzyme-refined. Neurological syndromes would, of course, be much rarer. They include cerebral, meningeal, myelitic, radicular, and neuritic forms, but much the commonest is a neuropathy of the fifth and sixth cervical roots. The large size of these roots relative to their intervertebral foramina makes them susceptible to compression. Miller and Stanton (1954) think that many roots may be involved in the reaction, but symptoms are confined to the few with anatomical factors in addition. If this is true and cortisone relieves the radicular swelling, it should prevent the ensuing paralysis. However, it failed in my case. Although, on October 2, 300 mg. of cortisone relieved root pains dramatically, paresis started later that

day and progressed rapidly to paralysis. Possibly, if cortisone had been taken at the onset of root pains, paralysis would not have occurred. As 75 mg. daily failed to prevent the pains on subsequent days, higher dosage would be needed for a period which presumably could be determined only by trial reduction and, if pains recur, resumption. Without cortisone, recovery occurs within a few months to two years, but 20% have residual weakness. Deaths are rare.

Prevention and treatment of serum reactions in general are admirably dealt with by Laurent and Parish (1952) and Williams (1955). Payling Wright and his colleagues (Littlewood *et al.*, 1954) have shown that, once injection of horse serum has been given, with second or subsequent injections the serum is likely to be removed so rapidly from the circulation by the liver that prophylactic effectiveness is curtailed. Therapeutic effectiveness would presumably be nil. However, they were referring to tetanus intoxication, which slowly increases over several days and therefore needs a persistent antibody for effective prophylaxis. Snake-poisoning is a sudden intoxication in which the venom circulates for a period before becoming fixed to susceptible structures. If antivenene is also circulating during these few minutes or hours—the fixation time of venom has not been investigated by modern methods—it should be able to neutralize significant amounts of venom. But if the patient has had a previous injection of horse serum there will be a race between the venom and the patient's horse-serum-precipitating antibodies for a coupling with the antivenene. The higher the concentration of the anti-horse-serum antibodies the more quickly would antivenene be destroyed.

Research is needed to decide if destruction occurs so rapidly that therapeutic efficacy would be impaired or nullified. If the latter proves to be the case it will be pointless to give antivenene obtained from horses to persons who have previously received an injection of any horse-serum antitoxin. Active immunization, as suggested for fishing folk exposed to risk of sea-snake bite (Reid, 1956), would be indicated. Whether such a procedure could be effective and practical is a matter requiring investigation.

Summary

A personal experience of neuropathic serum sickness following antivenene given for accidental sea-snake bite is recounted.

One hour after the bite the sea-snake yielded venom equivalent to 14 adult lethal doses, yet minimal poisoning followed the bite. The significance of this is discussed.

Contrast in theory and practice of first-aid measures is mentioned.

In the experience reported, the effects of treatment were much worse than those of the snake-bite. Antivenene is not harmless. It should not be regarded as mandatory in every case of snake-bite coming to hospital.

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SYSTEMIC TREATMENT OF TRICHOMONAL INFECTIONS

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It is generally agreed that the treatment of trichomonal infections is unsatisfactory. The claims made for various therapeutic agents are frequently conflicting, and this may be due to varying standards of diagnosis and criteria of cure as well as to faulty assessment arising from a high incidence of defaulters and difficulty in arranging a satisfactory series of controls. Recent work has established the fact that the parasite is often present in the urinary tracts of both male and female patients (Kean, 1955; Whittington, 1956, personal communication), and it seems reasonable to suppose that reinfection of the vagina after apparently successful local treatment may occur from this source. The ideal remedy for the disease would be a drug which would be effective when administered systemically and so would eradicate the parasite not only from the vagina in women and the urethra in men but also from other parts of the genito-urinary tract not accessible to local treatment. The investigation and treatment of sexual partners is also essential to eliminate another possible source of reinfection.

Recently claims have been made for two drugs which are said to be effective when administered by mouth. The object of this investigation was to test these claims and assess the place of these preparations in the treatment of trichomonal infections.

The first of these drugs was "trichomycin," an antibiotic isolated from *Streptomyces hachijoensis* in Japan by Hosoya *et al.* (1950, 1952). Reports from Japan indicated that it was effective against trichomonads both *in vitro* and *in vivo*. It was also claimed to be effective against *Candida albicans* (Magara *et al.*, 1955). Shortly afterwards another preparation, acinitrazole (2-acetyl-amido-5-nitrothiazole; "tritheon"; "trichorad"), was used in the United States (Cuckler *et al.*, 1955) and claimed to be effective when given by mouth in the treatment of trichomonal infections (Plentyl *et al.*, 1956).

Previously Bushby and Copp (1955) had demonstrated that certain of the amido-nitrothiazoles were more active *in vitro* against *Trichomonas vaginalis* than acetarsol; and Bushby, Catterall, and Williamson (1955) had shown that forminitrazole (2-formamido-5-nitrothiazole), a related compound, was effective in suppressing symptoms and causing the parasite to disappear rapidly when used as vaginal pessaries.

Diagnosis and Tests of Cure

In cases in the female, diagnosis was established by examination of wet smears and by cultures of vaginal secretions. Specimens of vaginal exudate were obtained, using the vaginal spoon method described by Jackson *et al.* (1948). Some of this material was inoculated into tubes of the liquid liver medium of Feinberg and Whittington (1957, in press). Samples of urine were obtained and the centrifuged deposit was examined microscopically and cultured in the same medium. In cases in the male, urethra scrapings were examined by dark-ground microscopy and cultures were also made. Centrifuged deposit of urine was also examined microscopically and cultures were taken. The patients were re-examined in the middle of the course of treatment and at the end of treatment, and the same tests applied. Samples of urine were obtained from a small number of patients on the last day of treatment and the antitrichomonal effect of the urine was assayed against standard cultures of trichomonads. In a few cases samples of blood serum were obtained before, during, and at the end of treatment, and the trichomonacidal effect was assayed. In many of the cases the blood haemoglobin was estimated and total white and differential cell counts were made before and after treatment.

Trichomycin

The first available supplies of trichomycin were in the form of vaginal pessaries containing 50,000 units of the antibiotic in each pessary. *In-vitro* tests of this substance against a standard culture of trichomonads showed that it was actively trichomonacidal in low concentration (Table I) and that its activity compared favourably with that of acetarsol (Table II).

TABLE I.—*In-vitro* Tests with Trichomycin

Final Concentration		After 1 Hour		After 6 Hours		After 24 Hours	
		Micro. Exam.	Culture	Micro. Exam.	Culture	Micro. Exam.	Culture
5,000 u./ml.	..	—	—	—	—	—	—
500 "	..	+	—	—	—	—	—
50 "	..	+	—	+	—	—	—
5 "	..	+	+	+	+	+	+
0.5 "	..	+	+	+	+	+	+

TABLE II.—*In-vitro* Tests with Acetarsol

Final Concentration		After 1 Hour		After 6 Hours		After 24 Hours	
		Micro. Exam.	Culture	Micro. Exam.	Culture	Micro. Exam.	Culture
10 mg./ml.	..	+	+	+	—	—	—
2 "	..	+	+	+	+	+	+
1 "	..	+	+	+	+	+	+

Twenty-three women were treated, each by the vaginal insertion of one pessary of trichomycin every night for 14 nights. As controls, 23 patients were treated with acetarsol, using two pessaries nightly for 14 nights. Eleven patients defaulted, of whom five were receiving trichomycin and six acetarsol. The remainder were followed for three months. Trichomonads disappeared from the vaginal secretions rapidly in both groups, but subjective relief of symptoms was more rapid in the group treated with acetarsol. One patient receiving trichomycin complained of vulval and vaginal soreness but completed the course of treatment. After follow-up for three months 17 of the patients treated with trichomycin had relapsed, eight of them within the first three