admission to hospital in September, 1958, the 24-hour urinary lead excretion was 110 μ g. and the concentration of lead in the blood was 70 μ g./100 ml. Like Case 6, this man was first treated with benzylpenicillin by mouth and intramuscularly in doses of 2 mega units. After a 48-hour interval penicillamine was given by mouth—0.5 g. for two days and 1 g. for two days (Table II).

Case 8.—A 50-year-old foundry worker who, when hospitalized in October, 1958, had a 24-hour urinary lead output of 150 μ g. and a blood lead reading of only 40 μ g./100 ml. Penicillamine was given by mouth; the dosage was 0.5 g. for two days and then, after a 24-hour interval, 1 g. for two days (Table II).

Discussion

In Cases 1–3 I.V. infusion of penicillamine thus produced a rise in the urinary excretion of lead of about the same order of magnitude as that caused by $\text{CaNa}_2\text{E.D.T.A.}$ Doubling or tripling of the dose of penicillamine brought about only a moderate increase in the output of lead when the penicillamine was given on consecutive days.

Cases 4 and 5 exemplify the simultaneous use of penicillamine and $\text{CaNa}_2\text{E.D.T.A.}$ in treatment of lead poisoning and the summation effect that may thereby be obtained. Of special interest was the finding from blood analyses that $\text{CaNa}_2\text{E.D.T.A.}$, in addition to its effect on urinary lead excretion, seemed to have a mobilizing action on lead stored in the body. This action was expressed as an increase in the blood lead after each infusion of $\text{CaNa}_2\text{E.D.T.A.}$ Similar observations were reported by Rieders *et al.* (1955). Penicillamine did not appear to have a corresponding effect.

In Cases 6 and 7 the urinary content of lead increased slightly in response to penicillin on the first day of therapy, but not on the second day. (This applied to peroral and intramuscular administration.) The second penicillin dose, on the other hand, was followed by a notable rise in the concentration of lead in the blood (Table II). The implications of this rise are as yet obscure.

Boulding and Baker (1957) stated that in two cases of lead poisoning they observed a significant increase of lead excretion in response to only 0.3 g. of penicillamine by mouth. Also in Cases 6, 7, and 8 of the present series low peroral dosage of penicillamine substantially increased the amount of lead in the urine. This effect was particularly striking if one takes into account the mildness of all three cases as judged from the blood content of lead—70, 70, and 40 μ g./100 ml. respectively—before treatment was begun.

Summary

In eight men with varying degrees of exposure to lead, penicillamine (β - β -dimethylcysteine) was tested as a chelating agent. The results were encouraging and were comparable with those given by $\text{CaNa}_2\text{E.D.T.A.}$ The two agents were also used in combination. Complexes of lead with dimercaprol or sodium calciumedetate ($\text{CaNa}_2\text{E.D.T.A.}$) have proved under certain circumstances to be nephrotoxic. Whether or not compounds of lead and penicillamine may have a similar action has not yet been elucidated. In the trials hitherto made no side-effects of any kind have been observed.

A good effect on the excretion of lead was observed in response to peroral as well as to intravenous administration of penicillamine.

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REFERENCES

- Belknap, E. L. (1952). *Industr. Med. Surg.*, **21**, 305.
Bessman, S. P., Ried, H., and Rubin, M. (1952). *Med. Ann. D.C.*, **21**, 312.
Boulding, J. E., and Baker, R. A. (1957). *Lancet*, **2**, 985.
Dudley, H. R., Ritchie, A. C., Schilling, A., and Baker, W. H. (1955). *New Engl. J. Med.*, **252**, 331.
Foreman, H., Finnegan, C., and Lushbaugh, C. C. (1956). *J. Amer. med. Ass.*, **160**, 1042.
Glömmé, J., and Swensson, A. (1956). *Svenska Läk.-Tidn.*, **53**, 753.
Karpinski, F. E., Rieders, F., and Girsh, L. S. (1953). *J. Pediat.*, **42**, 687.
Moeschlin, S. (1957). *Schweiz. med. Wschr.*, **87**, 1091.
Ohlsson, W. T. L. (1954). *Svenska Läk.-Tidn.*, **51**, 2324.
Rieders, F., Dunnington, W. G., and Brieger, H. (1955). *Industr. med. Surg.*, **24**, 195.
Siddbury, J. B., jun. (1955). *Amer. J. Med.*, **18**, 932.
Walshe, J. M. (1956). *Ibid.*, **21**, 487.

Preliminary Communications

In Pursuit of the Vector of Kala-azar in Kenya

The search for the vector of kala-azar in Kenya has continued for nearly ten years and it is only now that we may have found it. This paper should give an idea of the complexity of the problem. Two areas are involved: the Kitui focus south of the Tana River, where thousands of cases have occurred, and further west, in the Rift Valley, where the disease is sporadic.

FIRST SUSPECTS

The first sandfly to be suspected was *Phlebotomus clydei*, long regarded as a possible vector in the Sudan, where it bites man readily and has a geographical distribution corresponding to that of the disease. In Kenya *P. clydei* occurs mainly in gerbil burrows, but is occasionally present in the shafts of termite hills and other habitats; it only rarely bites man. In Kauriro, south of the Tana, *P. clydei* is naturally infected with a leishmania of lizards (*L. adleri*), which in the sandfly is morphologically indistinguishable from *L. donovani*; this at first confused us considerably. We are now convinced that *P. clydei* is not a vector in Kenya, even though a few specimens were infected by feeding them on a hamster just after a heavy culture of *L. donovani* had been inoculated into its skin (Heisch, 1954).

The next sandfly studied was a *Sergentomyia* named *P. garnhami*, which appears in enormous numbers about three weeks after the onset of rain, in the shafts of termite hills round Kitui; it bites man, though not very readily. *P. garnhami* was also infected artificially by feeding it on a skin lesion on the leg of a patient which swarmed with leishmaniae; only a small proportion developed leptomonads (5%), the infections being very light though present in the "anterior" station (Heisch, 1955). Sometimes *P. garnhami* was found naturally infected with "anterior" leptomonads; these never "took" in hamsters, and, like the *Leishmania* isolated from *P. clydei*, were probably derived from lizards.

P. garnhami is unlikely to be a vector in Kenya. Not only did none of our staff ever develop kala-azar after being severely bitten while studying its biting cycle near termite hills, but the species which is common during the rainy seasons round Kitui appears to be absent from the Rift Valley, where the disease is widely distributed and actually extending.

Another sandfly caught biting man in fair numbers near termitaries south of the Tana River, and in a beer-shop, in native huts, and in the bush near Marigat in the Rift Valley, is *P. schwetzi*. This sandfly, which belongs to the *minutus* group, is unlikely to be a vector; it quite often contains "anterior" crithidia, probably derived from lizards.

"MAJOR" GROUP

During these investigations we were frequently admonished by Professor Adler, who said we were on the wrong track, and that a sandfly of what used to be called the *major* group would prove to be the vector of kala-azar in Kenya as in other parts of the Old World. This made us look for *P. orientalis*, a sandfly of the *major* group, which bites man in the northern part of the Sudan and is probably a vector there (Kirk and Lewis, 1947). In Kenya a few specimens were collected in 1942 at Sericho, on the Uaso Nyiro River in the Northern Province, and one male was found in an empty gerbil burrow near Tseikuru, south of the Tana River, in October, 1954. An intensive search was made south of the Tana, in other parts of the Kitui district, and also in the Rift Valley, but no more were found; we concluded that *P. orientalis* is not a vector in Kenya. There was, however, a sandfly, fairly closely related to the *major* group and believed to be a new species, females of which were found in small numbers at Tseikuru and at Nuu, further south.

Specimens were obtained from a pit latrine, native huts, and termitaries, and a few were caught in the circle of light thrown on a table by a pressure lamp (Heisch, 1954). One female from a hut was freshly engorged, but the blood was not human, and at this stage none had been caught biting man. However, between January and May, 1955, 23 were taken on man near termite hills at Tseikuru; they bit readily, unlike *P. garnhami*, which bites man reluctantly even when present in large numbers. We now know, as confirmed by Dr. Parrot, of the Pasteur Institute, Algiers, that the elusive sandfly related to the *major* group actually comprises three distinct species of the subgenus *Synphlebotomus* Theodor, the females of which are identical, only the males being distinguishable. One is *P. martini*, another is *P. vansomeranae* (Heisch *et al.*, 1956), and the third is a new species as yet undescribed. All three occur chiefly in the ventilation shafts of termite hills, and the similarity of the females is most confusing, for when they come to bite man the only clue to their identity is the species of males predominating in the termitary at the time.

OBSERVATIONS AT KAURIRO

Some interesting observations were made at Kauriro, overlooking the Tana River and near Usueni Hill, in the vicinity of which many persons had contracted the disease. Africans are grouped in widely scattered village units containing about six huts in which live from 10 to 20 natives. A careful survey showed that Africans became infected only in some of these villages,

the number affected in a village being small; there seldom were more than four new infections in a year. The "safe" villages, where cases hardly ever occur, are sited in open ground, while "infected" villages are almost invariably near thickets of thorn bush. Sandfly catches, using man as bait, were carried out near termite hills in the open, and near termitaries within and on the edge of thickets. Usually only termitaries near the edge of thickets yielded sandflies of the subgenus *Synphlebotomus*, some emerging to bite man and others resting in the shafts; this marginal effect was very striking. Several marginal termite hills were selected for study, and it was soon discovered that *Synphlebotomus* sandflies come to bite in appreciable numbers for only two or three weeks after onset of the rains; they are then swamped and suddenly replaced by *P. garnhami*, which appears in enormous numbers. At Kitui there are two rainy seasons, one beginning in April, the other in October. Although *Synphlebotomus* sandflies are present throughout the year they are never numerous even at the time of the rains. Numbers sufficient for experimental purposes can be obtained only for about six weeks in the year.

Further observations were made between June 6 and 13, 1961. During this period 18 female *Synphlebotomus* flies were collected in the morning from six marginal termite hills at Kyamalutu, which is near Kauriro and about two miles (3 km.) east of Usueni Hill. One collected on June 10 was found to be naturally infected with flagellates in the anterior part of the mid-gut; these were inoculated into a hamster, even though at the time they were believed to be crithidia and not leptomonads. About six months later (December 20) the hamster was sacrificed and found to be heavily infected, numerous leishmaniae being present in smears from the spleen though they were absent from the skin. Of 28 male *Synphlebotomus* flies collected from termitaries at Kyamalutu in June, 1961, 21 were *P. martini*, the other seven being the undescribed species. The naturally infected female sandfly, therefore, was probably *P. martini*. It is not yet certain whether the strain isolated from the sandfly is *L. donovani*, and the next step is to test its pathogenicity in man. Professor Adler has studied the strain serologically and is convinced it is not *L. adleri*.

Several attempts to infect *P. martini* in the field by feeding it on patients with kala-azar have failed. This may have been because the sandflies were fed at stages of the disease when the patients were non-infective. It may be necessary to feed *P. martini* on early cases, when leishmaniae are present in the blood, rather than on late cases when the blood is negative, even though parasites are in the skin. In November, 1961, while watching *Synphlebotomus* feeding on a case of post-kala-azar leishmaniasis, it was noticed that the sandflies, which are rather delicately built, were unable to penetrate the thickened skin of the lesions containing leishmaniae, even though they fed readily on apparently normal skin. An examination of male sandflies from termitaries showed a great predominance of the third undescribed species of *Synphlebotomus*, the females of which probably feed in much the same way as those of *P. martini*. Of 66 specimens fed on a case of post-kala-azar dermal leishmaniasis one showed an "anterior" infection when dissected five days later. The flagellates were definitely leptomonads, but unfortunately they were not inoculated into a hamster or man, and so there is no way of deciding whether they were of human or

animal origin. In October, 1961, while one of us (D. J. B. W.) was in camp at Kauriro alone, and dissecting a number of what were presumably *P. martini*, he found a single specimen naturally infected with "anterior" leptomonads. These he inoculated into himself, but it is still too early to know what the result will be.

CONCLUSION

Our work is incomplete because (a) the strain of *Leishmania* isolated from the sandfly, though probably *L. donovani*, has not been finally identified, and (b) because all attempts to infect *P. martini* artificially by feeding it on patients have failed. This has prevented us from trying to transmit the infection to man by its bite. However, if the sandfly strain is eventually proved to be *L. donovani* the finding of what is probably an infected *P. martini* in nature will suggest that this species may be a vector of kala-azar in Kenya. It is also significant that of the three suspect *Synphlebotomus* species only *P. martini* has been found in the Rift Valley. It must be stressed that although the *Synphlebotomus* found infected in nature was probably *P. martini*, this is by no means certain, and the possibility that one or both of the other species may be vectors has not yet been excluded.

We would like to congratulate Drs. Strangways-Dixon and Lainson (1962), who in British Honduras not only infected a presumed vector *P. paraensis* by feeding it on a hamster previously inoculated with *L. brasiliensis*, but also transmitted the parasite to man by the infective bite of one of these insects.

Although in Kenya, at the right season, sufficient wild-caught females of *P. martini* and the other *Synphlebotomus* species are usually available for study, they can be induced to feed on infected hamsters only with difficulty and are then difficult to keep alive. Until *P. martini* and/or the other two species can be infected from a suitable animal or from man it will be impossible even to attempt transmission experiments.

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REFERENCES

- Heisch, R. B. (1954). *Trans. roy. Soc. trop. Med. Hyg.*, **48**, 449.
— (1955). *Nature (Lond.)*, **175**, 433.
— Guggisberg, C. A. W., and Teesdale, C. (1956). *Trans. roy. Soc. trop. Med. Hyg.*, **50**, 209.
Kirk, R., and Lewis, D. J. (1947). *Ibid.*, **40**, 869.
Strangways-Dixon, J., and Lainson, R. (1962). *Brit. med. J.*, **1**, 297.

The Prime Minister of Australia, Mr. MENZIES, said on May 2 that shortage of staff was one of the most acute factors limiting the admission of students to Australian Universities. He was replying to questions from Labour Members in the Australian Parliament. The Prime Minister said that a limit was placed on the number of students accepted in certain faculties in seven Australian universities this year. The quotas were determined by the facilities available in various years of the courses. It was estimated that 227 applicants had been rejected for the first year of the medical course at Sydney University, and 59 from the University of New South Wales. Ten were rejected from the second year of medicine at the University of Western Australia, including four south-east Asian students. (*Radio Australia News*, May 3.)

Medical Memoranda

Mercury Poisoning

Mercury gives off its vapour at room temperature, the amount rapidly increasing as the temperature is raised. When allowed to vaporize at normal room temperature volatilization of mercury reaches equilibrium far in excess of the maximum allowable concentration, which is 100 µg. per cubic metre of air (Sax, 1957).

There are three ways in which mercury may be absorbed by the body: inhalation of the vapour, absorption through the skin, and ingestion. The cases described occurred through spills of mercury over a period of several weeks.

CASE 1

About four weeks after starting work involving the use of mercury a patient attended with vague complaints of feeling unwell. On subsequent visits he appeared nervous and unduly jumpy, a condition called erethism. He complained of dizzy spells, insomnia, a metallic taste in the mouth, sore gums, burning in the throat, and looseness of the bowels. Later he developed pain across the front of the chest and in the region of both sacro-iliac joints. This was described as a boring pain in the bone. The urinary mercury was raised to 800 µg./litre. He found great difficulty in making decisions and felt he lacked his usual self-confidence. He was transferred to other work, out of contact with mercury, and was treated symptomatically. The main treatment given was to encourage fluid intake so as to increase the urinary output. The rationale is twofold—namely, to dilute the mercury excreted by the kidney to reduce renal irritation, and to assist natural excretion of mercury in urine. Since mercury is secreted in saliva he was encouraged to suck lemon sweets to stimulate salivation, then to spit into a suitable container. Mercury is excreted in saliva, urine, and faeces. Neither dimercaprol (B.A.L.) nor sodium calciumedetate (calcium disodium versenate, CaNa₂E.D.T.A.) was given, as the symptoms were not thought to be serious enough to warrant the risk of possible unpleasant side-effects from this treatment.

CASE 2

This patient, a colleague of Case 1, attended the surgery one afternoon in a state of extreme nervous exhaustion. He was sent home to rest in bed and came to see me on the following day. For the previous seven days he had been working very long hours. Prior to this he had been working the normal eight hours a day. When seen by me he complained of headache, insomnia, irritability, sore gums, nausea, and abdominal discomfort. He had become extremely nervous, with a marked tremor. The urinary mercury was raised to 400 µg./litre. Later he developed a blue line on the gum margin about 1 mm. from the base of the teeth. He said he had difficulty in judging distances. Owing to both this and the erethism he found it necessary to give up driving his car temporarily.

COMMENT

The manner appeared to be changed in both patients. In order to be able to observe slight changes it would seem important for examinations to be carried out by the same medical officer at regular intervals.

In addition to the various symptoms shown by the above cases previous authors (Hunter, 1955) have drawn attention to the fact that the patient's handwriting deteriorates owing to the increasing tremor.