precedes, and reaches its peak about a year before that of the trunk, so that during this period the proportion of leg to trunk with regard to total height would change. The height spurt as a whole is, however, due to a relative increase in the sitting height. Again, as the onset of the growth spurt is later in the male than in the female, the pre-pubertal differential growth rate continues to act for a longer time in the male, giving the relatively greater male limb length.

A comprehensive study of the growth of the long bones of the limb relative to height and sitting height has been made by Maresh (1943, 1955) in two age groups: birth to mid-childhood, and mid-childhood to maturity.

From the collected data she concludes (1) that there is not necessarily a uniform increase in bone length throughout childhood and adolescence—the growth rate may shift at any one time above or below the mean for the age group as a whole; and (2) that the change in growth rate need not affect all the long bones of the limb at the same time or to the same extent. Thus the relative bone lengths—that is, the percentage of height formed by the long bones—may vary throughout the growth period.

With the many variables affecting the length of a limb bone during growth, and in particular puberty, any estimate of height from immature bones is at best only an approximation. A further difficulty in this case was that we had to estimate the chronological age from skeletal age and therefore were unable to assess the chronological progress of the maturational status. We reported that the bones were part of the skeleton of a male age of from 12½ to 13½ years, with an estimated stature of 4 ft. 10 in. (147 cm.).

Eleven months before the discovery of the bones, in March, 1956, an orphan aged 13 years 11 months had been reported missing from an institution within the county. He had previously absconded for periods of three days and two days, and had been found living on shellfish in a cave on the first occasion, and in a barn, starving, on the second occasion. There was a record of his height and weight during the period January to April, 1954. The last height measurement was 4 ft. 5¼ in. (136 cm.). He had, however, grown 1¼ in. (3.2 cm.) in the preceding four months, and so it is reasonable to assume that he would have been 2 to 3 in. (5 to 7.5 cm.) taller when he disappeared in April, 1955. There was a dental record which corresponded to the dental condition as indicated by the eruption pattern and the dental casts.

Thus there was strong presumptive evidence sufficient to satisfy the authorities that the recovered bones were those of the missing boy. How he escaped notice living on the fringe of habitation, how he lived, and how long he survived on the hillside, will remain unknown.

The absence of all soft parts was probably in part a result of the prevailing subtropical conditions in the summer of 1955, and the scatter and partial destruction of the bones due to the action of indigenous mammals.

Summary

The assessment of the age, sex, and height was attempted from a collection of immature human bones consisting of a skull, mandible, loose teeth, and 128 separate bits of bone, some partially destroyed. The teeth were replaced in the jaws, dental casts were made, and the dental age was estimated from a consideration of the eruption pattern in the upper and lower jaws. The chronological age was estimated by consideration of the skeletal maturity, using as "markers" the presence/absence, union/non-union of secondary epiphyses. The sex was determined from the reconstructed pelvis and the condition of the teeth. The height was estimated from the length of the reconstructed left femur, right humerus, left tibia, and combinations of these three bones; and the difficulties of estimating the height from immature bones are discussed.

We are indebted to Dr. W. Gibson, of the Glasgow Dental Hospital, who made the dental casts and helped us in the analysis of the dental condition.

REFERENCES

Acheson, R. M. (1954). *J. Anat. (Lond.)*, **88**, 498.
—— and Hewitt, D. (1954). *Brit. J. prev. soc. Med.*, **8**, 59.
Clements, E. M. B., Davies-Thomas, E., and Pickett, K. G. (1953). ***Brit. med. J.***, **1**, 1421.
Greulich, W. W., and Pyle, S. I. (1950). *Radiographic Atlas of Skeletal Development of the Hand and Wrist.* Stanford Univ. Press.
Harding, V. S. V. (1952). *Child Develpm.*, **23**, 247.
Lancet, 1955, **2**, 384.
Lurie, L. A., Levy, S., and Lurie, M. L. (1943). *J. Pediat.*, **23**, 131.
Maresh, M (1943). *Amer. J. Dis. Child.*, **66**, 227.
—— (1955). Ibid., **89**, 725.
Meredith, H. V., and Knott, V. B. (1938). *Child Develpm.*, **9**, 49.
Simpson, S. L. (1948). *Proc. roy. Soc. Med.*, **41**, 192.
Speiger, B. (1950). ***Betekenis en Bepaling van de Skeletleeftijd*, p. 153.** With a summary and atlas in English. Leiden.
Spier, L. (1918). *Amer. Anthrop.*, **20**, 37.
Tanner, J. M. (1955). *Growth at Adolescence.* Oxford.
Todd, T. W. (1937). *Atlas of Skeletal Maturation* (Part I, Hand). London.
Washburn, S. L. (1946). *Anat. Rec.*, **95**, 353.

TREATMENT OF ASCARIASIS WITH VARIOUS SALTS OF PIPERAZINE

BY

L. G. GOODWIN, M.B., B.S.

AND

O. D. STANDEN, D.Sc.

From the Wellcome Laboratories of Tropical Medicine, London

Since the original observations by Boismare, cited by Fayard (1949), on the anthelmintic properties of piperazine, much has been published confirming the value of this drug in the treatment of ascariasis and enterobiasis. Numerous salts of piperazine have been used in attempts to improve upon the efficacy of piperazine hexahydrate, to render the various preparations more palatable, and to overcome the potential instability of hexahydrate solutions. Claims have been made concerning the greater efficacy of piperazine adipate over piperazine citrate in the treatment of whipworm (Dunn, 1955) which were not confirmed by Hucker and Schofield (1956), who demonstrated that piperazine citrate, adipate, phosphate, and sebacate were all inactive against this parasite; piperazine citrate has been shown to be inactive or only minimally active against *Taenia saginata* (Goodwin and Standen, 1957a); piperazine phosphate and piperazine adipate proved ineffective in the treatment of hookworm (Goodwin and Standen, 1957b).

The evidence is clear that while piperazine may possess minimal activity against other human helminths its great value in human medicine rests almost entirely in its high activity against *Ascaris lumbricoides* and *Enterobius vermicularis*. Hartley (1955) propounded an unsubstantiated theory that, owing to the deposition of adipic acid in the presence of gastric hydrochloric acid, piperazine adipate was less well absorbed in the stomach and therefore available to the worms in greater quantity in the small intestine than were piperazine salts of greater solubility. This claim was shown to be untenable in the light of laboratory experiments and observations on absorption and excretion in human volunteers (Standen *et al.*, 1955).

Against this background of claim and counter-claim made during the evaluation of piperazine as an anthelmintic it was decided that investigation should be made into the relative value of different salts of piperazine in the treatment of ascariasis under carefully controlled conditions of clinical trial. Also, since a single large

oral dose was desirable it was proposed to examine the more readily available preparations for greatest suitability under conditions of mass administration to native populations where certainty of dosage and speed of accomplishment present the two main factors in economy of drug and medical staff. The trials reported in this paper were carried out in Gambia during the months of August to October in 1955 and 1956.

Method

1955 Trials.—The object of these trials was the evaluation of the comparative activity of several salts of piperazine when given in equivalent dosage in terms of piperazine hexahydrate. The piperazine salts employed were the citrate, adipate ("entacyl"), phosphate, sebacate, and stearate. Citrate, phosphate, and sebacate were given in tablet form, each tablet being the equivalent of 500 mg. of piperazine hexahydrate. The adipate was also given in tablet form, each tablet containing the equivalent of 251 mg. of the hexahydrate. The bulky insoluble stearate was mixed with water and given as a draught. The patients treated were predominantly Bathurst schoolchildren between 5 and 11 years of age, but also included persons treated in villages or as out-patients at the Medical Research Council Hospital, Fajara, who ranged from under school age to adults. The drug was given as a single oral dose equivalent to 3 or 4 g. of piperazine hexahydrate and was followed by a small drink of water.

1956 Trials.—The object of the second trial was to evaluate the anthelmintic efficiency of piperazine when given as syrup of piperazine citrate ("antepar") in comparison with solid citrate and to determine whether the most advantageous method of mass treatment would be provided by a liquid or by a solid preparation. All the cases treated were Bathurst schoolchildren aged 5–16 years, none of whom had been treated the previous year. In all instances the drug was given in a single oral dose equivalent to 4 g. of piperazine hexahydrate. Three preparations were given: (*a*) freshly prepared, (*b*) stored for six months at 37° C., and (*c*) stored for six months at 50° C.

In both trials the diagnosis was made by observation of ascaris eggs in direct faecal smears, and a follow-up examination was done by the same method one week after treatment. Only children having large numbers of eggs in the stool were chosen for treatment. At follow-up the presence of a single fertile or infertile egg was counted as a failure to cure. All faecal smears were examined by us personally, all doses were given personally, and every mouth was opened and examined to ensure that the whole dose had been swallowed. The preparations were given in strict rotation regardless of age or sex.

Results

Between 40 and 60% of schoolchildren in Bathurst were found to be infected with ascarides. After treatment with piperazine worms were reported to have been passed by all but a very few children. The numbers of worms varied between 1 and 90, a figure between 10 and 20 being the most common.

1955 Trials

A total of 386 Africans with ascariasis were given a 3-g. dose and a further 56 were given a 4-g. dose equivalent of piperazine hexahydrate. The distribution and results of treatment for each salt are given in Table I. The inequality in the number of cases treated with each salt is accounted for by failure to present for follow-up examination after treatment and by limited supplies of the sebacate and stearate.

In 77 cases treated with piperazine citrate, 103 with piperazine phosphate, and 92 with piperazine adipate at the 3-g. level the results were remarkably uniform at 76% absolute clearance in each group. These three salts were equal in activity regardless of their different solubilities. At the 3-g. dose level the clearance rate with sebacate and stearate was somewhat higher, but the numbers of people treated were smaller and the difference therefore not highly significant.

TABLE I.—*Results of Treatment with Different Salts of Piperazine Given as a Single Oral Dose to 442 Cases of Human Ascariasis*

	3-g. Dose of Piperazine Hexahydrate Equivalent					4-g. Dose of Piperazine Hexahydrate Equivalent	
	Citrate	Phosphate	Adipate	Sebacate	Stearate	Phosphate	Adipate
No. treated	77	103	92	58	56	28	28
No. cleared	59 (76%)	78 (76%)	70 (76%)	50 (86%)	48 (86%)	25 (89%)	23 (82%)

Only 56 cases were treated at the 4-g. level. Of 28 treated with piperazine phosphate 25 were cleared absolutely compared with 23 out of 28 for the adipate. The difference between 89 and 82% clearance respectively is not significant. Nevertheless, it would appear that the 4-g. dose of piperazine cleared about 10% more cases than the 3-g. dose of equivalent salt and equalled the 3-g. dose of sebacate or stearate.

1956 Trials

A total of 328 schoolchildren with ascariasis were treated with piperazine citrate syrup or solid piperazine citrate in tablet form. Of these, 91 were given 4-g. equivalents of solid piperazine citrate, 44 were given piperazine citrate syrup stored for six months at 50° C., 99 were given the syrup stored for six months at 37° C., and 94 received freshly prepared syrup that had not been subjected to tropical temperatures except for the short duration of the trials. In all instances the dose of piperazine was the same. The results are given in Table II.

TABLE II.—*Results of Treatment of 328 Cases of Human Ascariasis with Piperazine Citrate Given as Solid and Liquid Preparations in Single Oral Dosage Equivalent to 4 g. of Piperazine Hexahydrate*

	Solid Piperazine Citrate	Piperazine Citrate Syrup (Antepar)		
		Stored for 6 Months at 50° C.	Stored for 6 Months at 37° C.	Fresh
No. treated	91	44	99	94
No. cleared	76 (84%)	38 (86%)	87 (88%)	82 (87%)

Very uniform results were obtained whether piperazine citrate was given as the solid or as the syrup, and no significant difference was observed between the activity of fresh syrup and that of syrup which had been subjected to high or abnormally high storage temperatures for six months. A mean clearance rate of 86.25% was obtained in 328 cases of ascariasis treated with piperazine citrate; 84% were cleared with the solid preparation and 86, 88, and 87% were cleared respectively with piperazine citrate syrup when the syrup was used after storage for six months at 50° C., at 37° C., or fresh.

The large dose of 4 g. of piperazine was used in order to obtain a maximal clearance rate from a single treatment.

Apart from two instances of nausea and vomiting which occurred immediately after swallowing the bulky soapy suspension of stearate, we observed no toxic effects of any kind, nor were there any complaints from the children or their parents. This is of particular interest in view of the large number of children treated, and because immediately before the 1956 trial there had been a widely known incident in Bathurst in which a child had died after a dose of oil of chenopodium, administered for the treatment of roundworm infection.

Discussion

It is seen from the results of the 1955 and 1956 trials on 770 cases of ascariasis that the comparative efficiency of piperazine given as citrate, adipate, or phosphate showed no significant variation with the salt employed. The dose response in terms of absolute clearance was very similar, being 76% for the 3-g. dose and 82–89% for the 4-g. dose. Similarly, the effectiveness was the same whether the citrate was given as a solid or as a liquid preparation. In 58 and 56

cases treated with piperazine sebacate and stearate respectively, the dose-response for a 3-g. equivalent of piperazine hexahydrate was equal to that of a 4-g. dose of citrate, adipate, or phosphate.

From a series of trials where the number of patients treated was large enough to cover individual variation it is clear that the effectiveness of piperazine is not influenced by the choice of salt except perhaps in the case of the salts of high molecular weight such as the sebacate and stearate. Consequently it is of interest to discuss the relative merits of the different preparations in terms of suitability for administration to native populations where ascariasis is of public-health importance and where mass treatment is the logical method of combating infection.

Considerable differences were observed in the reaction of patients to taking large oral doses of solid preparations. To achieve a single oral dose of 4 g. of piperazine the patient had to swallow eight tablets of citrate, phosphate, or sebacate, 16 tablets of adipate, or a bulky draught of stearate. Because of the large size of the molecule of sebacate and stearate the bulk of the 4-g. dose made administration difficult and clumsy. Since most of the patients were unused to swallowing tablets the medicines were mostly chewed. In this connexion, taste played a considerable part in acceptability. The solid citrate and phosphate were apparently acid but not unpleasant, the adipate was distasteful, and the sebacate more so. The stearate was tasteless but soapy and bulky, and occasionally produced vomiting after treatment.

Because of the large dose of drug required it appeared that all compressed preparations suffered from the disadvantage of the necessity for consuming many tablets. Frequently one or more of the tablets would be dropped and had to be recovered, and careful watch had to be maintained because a proportion of the dose of the less pleasantly flavoured salts sometimes migrated to shirt pockets for subsequent disposal. Also, the flow of saliva did not seem to be very great and some of the solid preparations had a tendency to stick to the teeth. The adipate and sebacate were particularly difficult in this respect, the phosphate less so, and the citrate, having a more acid flavour which stimulated salivation, hardly at all. These characteristics made strict control of the trials a lengthy and tedious business. In contrast, the use of a fluid preparation, such as syrup of piperazine citrate, reduced the time of administration to a marked degree. The use of syrup as a vehicle also made the drug easy to give to infants. One of the disadvantages that might be anticipated in the use of fluid preparations of piperazine salts in the tropics is the possibility of instability. This proved unjustified in view of the fact that piperazine citrate syrup stored for six months at temperatures above those usually encountered showed no indication of reduced efficiency and was apparently unaffected except for some degree of darkening in the sample stored at 50° C.

It was concluded from the trials that the efficiency of piperazine in the treatment of ascariasis is not influenced by the nature of the salt where this is citrate, adipate, or phosphate; that the sebacate and stearate are slightly more efficient at the 3-g. dose level but are impracticable in use on grounds of objectionable taste or bulk. It has also been shown that piperazine citrate syrup was as effective as the solid citrate when given at the equivalent dose of piperazine base. It can thus be established that the effectiveness of piperazine preparations is almost entirely dependent upon the piperazine content of the salt, whichever may be employed. It was also found that the piperazine citrate syrup was of greater practical use than solid preparations for mass treatments because of the economy in time and labour when employed in large-scale administration.

Summary

In two successive trials in the Gambia 770 cases of human ascariasis were treated with piperazine preparations given as a single large oral dose.

With piperazine citrate, adipate, and phosphate a dose equivalent to 3 g. of piperazine hexahydrate gave clearance in 76% of cases treated; a 4-g. equivalent gave clearance in 82–89%.

Piperazine sebacate and stearate gave clearance in 86% of cases given a 3-g. equivalent of piperazine hexahydrate but were impracticable in use on grounds of taste or bulk.

It was established that the efficiency of piperazine preparations is directly related to the content of base and is little influenced by the nature of the salt.

Piperazine citrate syrup was found to be stable at elevated temperatures, to be as effective as solid citrate, adipate, or phosphate, and to be of more practical value than tablet preparations in mass treatment on grounds of rapidity of dosage, rigidity of control, and palatability.

No toxic side-effects were observed after a single dose of 4 g. of piperazine.

We wish to acknowledge the hospitality of the Medical Research Council, who placed the facilities of the M.R.C. Research Laboratories, Fajara, at our disposal, and to extend our thanks to Dr. I. A. McGregor, Director, for his invaluable co-operation. We are also indebted to Dr. S. O. Jones, Director of Medical Services, Gambia, and to Mr. Jack Forrest and Mr. Don Blakeby, of the Education Department. We are particularly pleased to record our thanks to Miss Elizabeth Browning, Education Organizer, without whose assistance the work could not have been completed in the time available.

REFERENCES

Dunn, T. L. (1955). *Lancet*, **1**, 592.
Fayard, C. (1949). Thèse, Paris, No. 889.
Goodwin, L. G., and Standen, O. D. (1958a). *Brit. med. J.*, **1**, 133.
—— —— (1958b). Ibid., **1**, 135.
Hartley, F. (1955). Ibid., **2**, 205.
Hucker, A. G., and Schofield, F. D. (1956). Ibid., **2**, 1159.
Standen, O. D., Goodwin, L. G., Rogers, E. W., and Stephenson, D. (1955). Ibid., **2**, 437.

PIPERAZINE AND MALE FERN IN EXPULSION OF TAPEWORMS

BY

L. G. GOODWIN, M.B., B.S.

AND

O. D. STANDEN, D.Sc.

From the Wellcome Laboratories of Tropical Medicine, London

In spite of a number of claims for the efficacy of alternative treatments, the generally most reliable and cheap drug for the expulsion of tapeworms is extract of male fern. When used with care this may be given with safety, and provides a fair measure of success. There are conflicting reports concerning the efficacy of piperazine against tapeworms; Shafei (1955) reports cure in 50% of cases infected with *Hymenolepis nana*, while Nagaty *et al.* (1955) found piperazine ineffective against this cestode and also against *Taenia saginata*.

While working in the native hospital at Mwanza, Tanganyika, in 1954, we tried the effect of piperazine citrate (" antepar ") tablets on three patients harbouring *Taenia saginata*. A single large dose, equivalent to 4 g. of piperazine hexahydrate, was given and was followed 20 hours later by a purge (2 oz. (60 g.) of magnesium sulphate). All stools passed during the next 24 hours were collected and examined. All three patients passed 2–3 ft. (60–90 cm.) of gravid proglottids, but no small proglottids from nearer the head were seen. Although the drug appeared to affect the worm to some degree, it was clear that the greater part remained. Each of the