Bull. World Hlth Org. } 1953, 8, 107-122
Bull. Org. mond. Santé }

ANTIBIOTICS OTHER THAN PENICILLIN IN THE TREATMENT OF YAWS

KENNETH R. HILL, M.D.

Professor of Pathology,
University College of the West Indies, Jamaica
Formerly Consultant, Treponematoses Control Project in Indonesia, World Health Organization

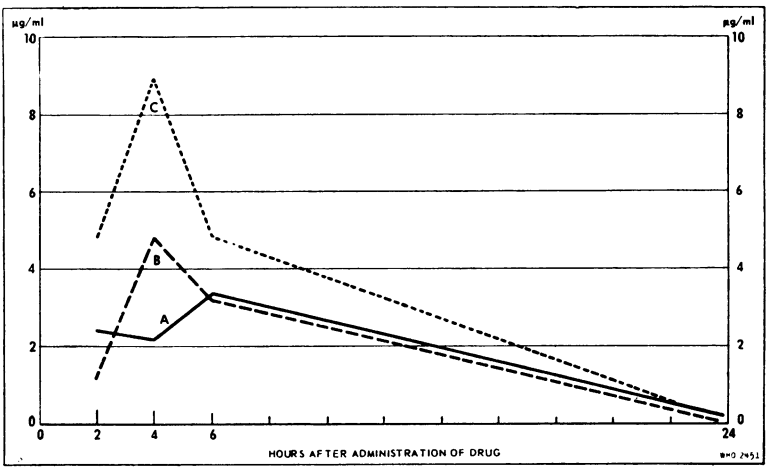
Since Findlay in 1943 [18] first used a crude preparation of penicillin to treat framboesia in West Africa, the reputation of the use of penicillin in the treatment of this disease has increased with the passing of the years.[7, 11, 14, 18, 19, 25, 28, 37]

Since 1947 three new antibiotics have been isolated from strains of *Streptomyces* species isolated in widely separate places. They are chloramphenicol, described by Ehrlich et al.,[13] aureomycin, described by Ehrlich et al.[13] and by Duggar,[10] and, more recently, terramycin, described by Finlay et al.[15] All three antibiotics are characterized by a wide antimicrobial activity against many bacteria as well as against certain rickettsiae, large viruses, and treponemes.

Although some difference in activity may be demonstrated both in vitro and in vivo by these three antibiotics, they have much in common. All three have a low degree of toxicity to both animals and man, and all three at proper dosage levels are equally effective in certain diseases of man. All three drugs are crystalline, efficacious when taken by mouth, rapidly absorbed, and excreted in relatively large quantities in the urine. From the clinical point of view, these drugs differ from each other in that one is more effective than another against certain diseases; for example, chloramphenicol against typhoid fever, terramycin against certain rickettsioses, and aureomycin against certain staphylococcus infections.

In Jamaica, the dosage aimed at was approximately 25 mg of antibiotic per kg of body-weight per day. This, in fact, implied a dosage of 1 g per day for 14 days for the adult. The subsequent description, taken from the publication by Welch,[36] of absorption and excretion will be in relation to the effects of this 1-g dose on an adult person. Fig. 1 shows the average serum levels following one 1-g oral dose of terramycin, aureomycin, and chloramphenicol. It will be noticed that significant blood concentrations are present for at least 6 to 8 hours after administration of all the drugs,

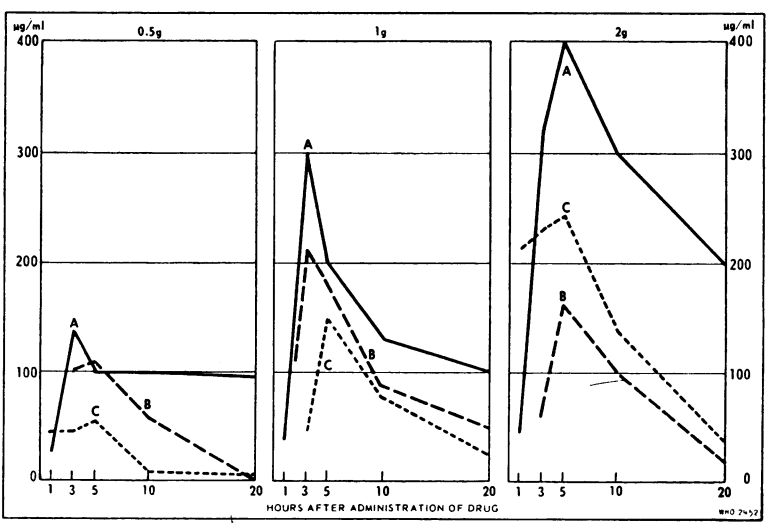
FIG. 1. AVERAGE SERUM LEVELS FOLLOWING 1-g DOSE OF TERRAMYCIN, AUREOMYCIN, AND CHLORAMPHENICOL



A = Terramycin B = Aureomycin C = Chloramphenicol

and there is, up to about 24 hours, still some concentration in the blood. It should also be noted that chloramphenicol and aureomycin seem to be more rapidly absorbed.

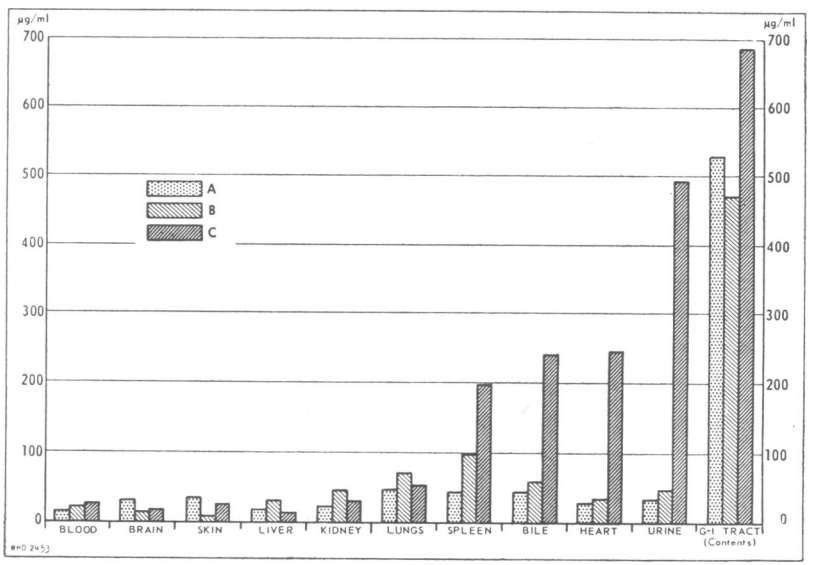
FIG. 2. AVERAGE CONCENTRATIONS OF TERRAMYCIN, AUREOMYCIN, AND CHLORAMPHENICOL IN URINE AFTER SINGLE ORAL DOSES



A = Terramycin B = Aureomycin C = Chloramphenicol

Fig. 2 shows the urinary concentration of terramycin, aureomycin, and chloramphenicol after a single oral dose of 1 g, and it will be noticed that the urine still contains a certain quantity after a 1-g dose at the end of 20 hours. This implies that there is still a concentration within the body after that time. Fig. 3 shows the distribution of the same drugs in rabbit tissues 4 hours after an oral dosage with half a gram of each drug. These experiments therefore show that the absorption is rapid, that there is still a certain amount of drug being excreted at the end of 20 to 24 hours, and that the drug does enter the skin tissues.

FIG. 3. DISTRIBUTION OF AUREOMYCIN, TERRAMYCIN, AND CHLORAMPHENICOL IN RABBIT TISSUES FOUR HOURS AFTER ORAL ADMINISTRATION OF 0.5 g PER kg BODY-WEIGHT



A = Terramycin B = Aureomycin C = Chloramphenicol

I am unaware of any experiments which would indicate the therapeutic levels desirable in either blood or tissues for these antibiotics against treponemes such as have been carried out by Eagle et al.[12] on penicillin.

One encouraging feature of these antibiotics is that their pattern of resistance is of the penicillin type and not of the streptomycin type.[5] The cause of bacterial resistance to antibiotics appears to be the occurrence of spontaneous mutants present among a large population of cells.

There are two known types of bacterial resistance to antibiotics. The penicillin type requires a series of multiple genetic changes for development of complete resistance. Complete resistance is never attained by a single mutation and requires the interaction of a series of consecutive mutations;

in the streptomycin type, complete resistance may be brought about either gradually, by a series of multiple mutations, or at once, by a simple genetic change. Antibiotics which have the pattern resistance of the penicillin type are, therefore, unlikely ever to produce a resistant type of organism in man.

As regards the daily dosage of these antibiotics in the Jamaica surveys, an approximate estimate was made of about 25 mg per kg of body-weight. This actually implied in practice that for the adult the dosage was four capsules per day (1 g) for 14 days; for the 5- to 10-year-old child, two capsules per day (0.5 g) for 14 days; and for the small baby or child up to 5 years old, one capsule per day (0.25 g) for 14 days.

Aureomycin

Several authors have reported on the efficacy of aureomycin in treponemal infections, especially in syphilis.[26,30] Table I shows the use of aureomycin in the treatment of yaws by various workers.[a] Ampofo & Findlay,[1,2] using a dosage of 0.75 g per day for seven days, with a follow-up varying from six weeks to six months, found a clinical cure in all cases; in two patients tested for six months, the Kahn serological test was found to be negative in one and doubtful-positive in the other.

Loughlin et al.[24] and Schaeffer et al.,[33] working in Haiti, have reported trials of the drug on a much larger scale. After some preliminary experimental trials, they came to the conclusion that a total dose of 10 g of aureomycin

TABLE I. TREATMENT OF YAWS WITH AUREOMYCIN

Author	Number of cases	Dosage	Duration of follow-up	Toxicity	Result
Ampofo & Findlay [1,2] (West Africa)	7	up to 0.75 g daily × 7	up to 6 months	nil	clinical cure
Loughlin et al.[24] (Haiti)	100	Total = 10 g : (*a*) 2 g daily × 5 (*b*) daily doses of 5 g, 3 g, and 2 g	approximately 3 months	2 cases of nausea and vomiting	clinical cure (2 relapses)
Hill et al.[20] (Jamaica)	10	25 mg per kg of body-weight daily × 14	1 year	occasional nausea	clinical cure
Hill [18] (Jamaica)	41	25 mg per kg of body-weight daily × 14	9-12 months	occasional nausea	clinical cure

[a] It is regretted that the work of Lins et al.[22] in Brazil could not be included here.

would render all the infectious cases non-infectious; and they established two schedules : 10 g in five days and 10 g in three days. Both these schedules appeared to give equally good results on short-term follow-ups of about three months. They have treated about 100 cases with the two schedules and have had only two relapses.

In Jamaica, my colleagues and I [18, 20] treated 41 patients with 1, 2, 3, or 4 0.25-g capsules daily for 14 days; occasionally, infants were treated with a chocolate-tasting powder-form. Our results may be summarized as follows :

	After 1 month (%)	*After 9-12 months* (%)
Follow-up	81.5	50.5
Cure	70.0	82.5
Improvement	28.5	—
Failure	—	10.0
Relapse	1.5	5.0
Reinfection	—	2.5
Delinquency	18.5	49.5

As regards the clinical course following treatment, it was found that the healing was generally much slower than in the case of penicillin. This has been observed by others,[1] although Loughlin et al.[24] found the contrary to be true. The initial lesions and the early framboesides cleared up very quickly, but the later ulcerative and lupoid framboesides sometimes took as long as from six weeks to six months to heal completely. The non-ulcerative plantar framboesides became painless within the first week or so, but because of the hyperkeratosis they took months to show any marked clinical improvement. Several cases showing large ulcerative framboesides were treated beneficially by the topical application of aureomycin powder or aureomycin dressings as well as by oral administration of the drug. Similar successful results have been reported by Loughlin et al.[24]

One interesting finding in Jamaica, which was observed in ten cases in which initial framboesial ulcers or later ulcerative framboesides were present, was that between the first and second week the healing crusts became chalky-white in colour. Subsequent healing seemed to be quite normal. No signs of toxicity other than occasional nausea were encountered.

As an example of a case in which treatment failed, the following can be given :

Case A37 : female aged two years ; duration of disease, four months; papillomatous framboesides present; serological titre, 1,024 Kahn units; dosage, 0.25 g daily for 14 days. After four weeks, the titre had fallen to 256 units with only slight clinical improvement. After nine months the patient was no better, and the titre remained at 256. Comment : there was great doubt whether the total dosage of drug had been administered.

Several cases showed reinfection after cure :

Case A50 : female aged seven years ; duration of disease, four months ; plantar and palmar ulcerative framboesides present ; serological titre, 16 Kahn units ; dosage, 0.5 g daily for 14 days. Two weeks after treatment she showed slight improvement ; four

weeks after treatment the improvement continued, with a titre of 8 units. After nine months she was seronegative and completely cured, but four weeks later she was bitten by a dog and developed an initial lesion at the site of the bite.

Case A34 : male aged three and a half years ; duration of disease, 11 months ; macular framboesides present, and pains in the bones of the hands and legs; serological titre, 256 Kahn units; dosage, 0.5 g daily for 14 days. After two weeks the serological titre was 138 units, and the patient was clinically cured; after four weeks the titre had dropped to 32 units. After nine months a history was given that the child had been free from infection until just a month before when he had contracted an initial lesion. On examination he was found to have an initial lesion and macular framboesides; his serological titre at that stage was 128 Kahn units.

Chloramphenicol

Chloramphenicol has been shown to have some activity against the treponeme of syphilis.[29, 31] Table II gives data on the use by several authors of chloramphenicol in the treatment of yaws.

Ampofo & Findlay [3] in Africa treated three patients and, after a six-week follow-up, found a clinical cure in all cases. Payne et al.,[27] trying various schedules of dosage on ambulatory and hospital patients, treated 62 cases with success; but there was only a short follow-up of six weeks.

TABLE II. TREATMENT OF YAWS WITH CHLORAMPHENICOL

Author	Number of cases	Dosage	Duration of follow-up	Toxicity	Result
Ampofo & Findlay [3] (West Africa)	3	1.5 g, 2 g, or 3 g daily × 7	6 weeks	nil	clinical cure
Payne et al. [27] (South America)	62	total of 3 g - 16 g on various schedules	6 weeks	nil	clinical cure and improvement in many cases
Hill [18] (Jamaica)	99	25 mg per kg of body-weight daily × 14	9-12 months	occasional nausea and vomiting ; thirst	clinical cure 79 %

In Jamaica, my colleagues and I [18] have treated 99 cases, using a dosage of 25 mg per kg of body-weight per day for 14 days, and the follow-up has been 9 to 12 months. At the end of one month, the delinquency rate was 15%; and, at the end of 9 to 12 months, 17%. The area involved was much easier to administer from the point of view of the patients than that in which we tested the aureomycin, and we had a bigger staff of nurses and sanitary inspectors. The delinquency rate was therefore much lower than in the aureomycin trial. Occasionally, patients had felt nauseated after taking the drug, but otherwise no symptoms of toxicity were reported. The results were as follows :

	After 1 month	*After 9-12 months*
	(%)	*(%)*
Follow-up	85.0	83.0
Cure	65.0	79.0
Improvement	35.0	—
Failure	—	3.5
Relapse	—	13.0
Reinfection	—	4.5
Delinquency	15.0	17.0

The following may be cited as typical cases of failure :

Case A5 : male aged seven years ; duration of disease, unknown ; circinate papillomatous and papular framboesides present ; serological titre, 256 Kahn units ; dosage, 0.5 g daily for 14 days. In two weeks he had improved clinically, but there was no change in the titre ; in four weeks all lesions had disappeared, but the titre was still the same. After nine months the titre had dropped to 16 units, but he had developed bilateral tibial osteitis.

Case C77 : male aged ten years ; duration of disease, six months ; non-ulcerative plantar framboeside present ; serological titre, 128 Kahn units ; dosage, four capsules (1 g) daily for 14 days. In two weeks he had improved, with a titre of 64 units. In four weeks the titre was unchanged ; after nine months the patient's condition was much the same, with a positive serological reaction.

Several cases showed relapse; the following may be considered as typical :

Case C7 : female aged 12 years ; disease of long duration ; papillomatous framboesides present ; serological titre, 32 Kahn units ; dosage, 0.5 g daily for 14 days. After two weeks she had improved but her titre was still 32 ; after four weeks the improvement had continued and the titre had fallen to 16 ; after six weeks all lesions had disappeared, and the titre was 8. Nine months after treatment she relapsed, with a titre of 256 Kahn units and ulcerative and lupoid framboesides of the legs.

Cases of reinfection also occurred :

Case C69 : female aged nine years ; duration of disease, one and a half months ; circinate framboesides and non-ulcerative plantar lesions present ; serological titre, 64 Kahn units ; dosage, 0.25 g daily for 14 days. In two weeks she had improved, and her titre was 32 ; after four weeks she was clinically cured but with no change in titre. Another member of her family contracted yaws, and the patient was reinfected. Nine months after treatment, she had ulcerative plantar framboesides and her titre was 80 Kahn units.

In general, the healing of the framboesial lesions was similar to that following treatment with aureomycin.

Terramycin

Terramycin has been shown to act as a curative agent in human syphilis by Hendricks et al.[17] and Schoch & Alexander.[34] It has also been shown

experimentally by Levaditi & Vaisman [21] to have an anti-treponemal action in syphilitic rabbits and mice. The authors conclude that this drug comes close to penicillin in its curative effects; that is to say, it brings about rapid disappearance of the treponemes, cicatrization of the lesions, and sterilization of blood and lymph-nodes. They are also of the opinion that aureomycin and chloramphenicol are not as virucidal in their action.

TABLE III. TREATMENT OF YAWS WITH TERRAMYCIN

Author	Number of cases	Dosage	Duration of follow-up	Toxicity	Result
Guimarães & Travassos [16] (Brazil)	4	total of 5 g-15 g over 10 days	16 days	—	clinical cure
Loughlin & Joseph [23] (Haiti)	150	(*a*) 7 g in 3 days (*b*) 10 g in 5 days	approximately 3 months	nausea, vomiting, and anorexia in 5 cases	clinical cure
Ampofo & Findlay [4] (West Africa)	6	1.5 g-2 g daily × 7	3 months	nil	clinical cure
Hill [18] (Jamaica)	8	25 mg per kg of body-weight daily × 14	3 months	intense thirst	clinical cure in 5 cases

Table III gives data on the use of terramycin by several authors in the treatment of yaws. It will be seen that, in Brazil, Guimarães & Travassos [16] successfully used terramycin in four cases with total doses of 5 g-15 g over a period of ten days; active lesions cleared in 6-16 days. Ampofo & Findlay, [4] working in West Africa, treated six patients with secondary yaws with doses of from 10.5 g to 14 g over a period of seven days. The treponemes disappeared from the lesions in 24-36 hours, and there was healing within four days. A three-month follow-up showed no recurrence.

The most extensive trial has been that of Loughlin & Joseph,[23] in Haiti, who have treated 150 cases of yaws. The patients consisted of adults and children presenting primary lesions, secondary lesions, and tertiary manifestations, all seropositive. They were given the following oral treatment : 7 g in 3 days (3 g on the first day, 2 g on the second, and 2 g on the third), or 2 g daily for a period of five days (total dosage 10 g). Their results were as follows : rapid disappearance of the treponemes from the lesions in 24 hours, prompt cicatrization of the lesions, striking improvement of the patient's general condition, and an extremely low incidence of relapses (2 cases out of the first 65 cases treated by the three-day regimen).

Primary lesions were often almost completely healed in four days and the deeply ulcerative initial lesions within three weeks. Secondary lesions

were healed in 5-14 days and ulcerative plantar lesions in 11-21 days. Tertiary lesions responded well, albeit more slowly; and, with the addition of the local application of terramycin powder to large ulcerative and secondarily infected lesions, the rehabilitation of a number of patients, who might otherwise have been considered as hopeless cripples, was accomplished. Nausea, vomiting, and anorexia were noted in five children under eight years of age.

The authors are of the opinion that terramycin is much more efficacious than procaine penicillin in dosages of 600,000 to 1,200,000 units, even in children, and that it has a superior curative action not only in the treatment of primary and secondary yaws, but also in the treatment of tertiary yaws, especially when used in conjunction with topical therapy.

In Jamaica we have studied the effects of terramycin in eight cases only, over a period of three months. It will be seen from table IV that five cases out of the eight were cured by the end of three months. The other three cases, which had non-ulcerative plantar lesions, were much improved at the end of three months; they had all very quickly lost their pain, were able to walk, attend school, or go back to work. All patients complained of thirst.

Serology

The following tabulation shows the serological findings, following treatment with aureomycin and chloramphenicol, using the Kahn quantitative test; the pattern is almost the same for both drugs :

	Aureomycin (41 cases) (%)	*Chloramphenicol (81 cases) (%)*
Cases with fall in titre	78	80
Cases with no fall in titre	18	10
Seronegative cases remaining seronegative	4	10
Cases becoming seronegative	25	29
Cases with rise in titre two weeks after treatment, with subsequent fall	12	12

The titre of the reagin in framboesia in general tends to rise much more slowly than that in syphilis after initial infection; likewise, after treatment, the fall in titre in the framboesial patient is much slower. Thus, Chambers [6] reports that, out of 554 cases of framboesia treated variously with arsenicals and bismuth compounds, only about 54% had a reversal of the serological findings after 18 months; and Saunders et al.[32] found that, after two and a half years, of 1,265 cases treated with neoarsphenamine, only about 60% had become seronegative; and that, out of 535 cases treated with bismuth salicylate, only about 72% had become seronegative.

TABLE IV. TREATMENT OF YAWS WITH TERRAMYCIN IN JAMAICA, 1951-2

Case no.	Age in years	Duration of infection	Type of lesion	Dosage	Time taken for cure	Clinical condition after 3 months
T1	28	1½ years	non-ulcerative plantar framboeside (had been "cured" with chloramphenicol but relapsed)	0.25 g × 14	—	lesions still present but tenderness gone
T2	12	2 months	initial lesion	0.5 g × 14	2 months	cured
T3	12	3 months	initial lesion and papillomatous framboeside	0.5 g × 14	?	cured
T4	35	?	non-ulcerative plantar framboeside	1 g × 14	—	lesions still present but tenderness gone
T5	7	6 months	non-ulcerative plantar framboeside	0.5 g × 14	—	lesions still present but tenderness gone
T6	3½	1 year	initial lesion and macular framboesides, and non-ulcerative plantar framboeside	0.25 g × 14	At 1 month all cured except plantar lesion	cured
T7	10½	3 years	ulcerative plantar framboeside	0.5 g × 14	—	cured
T8	9	2 months	initial lesion, and macular and papillomatous framboesides	0.5 g × 14	14 days	cured

Hill et al.[19] found very few serological reversals to negativity in their series of cases after treatment with repository penicillin, and they quote similar findings by other authors.

In the present study, although a decrease in the titre of the reagin was to be expected one year after treatment, it is significant that, of the originally seropositive cases, 78% of those treated with aureomycin and 80% of those treated with chloramphenicol should have had a remarkable drop in titre almost approaching seronegativity, and that 25% and 29%, respectively, of the total cases should actually have become seronegative.

Another point worthy of note is that 12% of all cases showed a temporary rise in titre with the serological test two weeks after treatment. This finding is not unknown in syphilis and is probably due to an extra stimulation of the production of reagin during an active phase of the disease.[35] The majority of cases under study had a duration of infection of from 1 to 12 months and therefore were in the early stages of the disease.

Discussion

In these trials there has been little sign of toxicity with these drugs other than occasional nausea. As regards ease of administration, it would seem superficially that oral therapy is ideal; and, certainly from the point of view of pain, the patients much prefer not to have an injection. Unfortunately, it is found in practice that the swallowing of the capsules by children is a very difficult procedure; the giving of capsules every day for 14 days has proved most difficult from both an administrative and a supervisory point of view. However, aureomycin may be given in chocolate-tasting powder-form, and chloramphenicol as a palatable liquid palmitate, which have proved of benefit.

The team engaged in the recent trial in Jamaica made a special effort to see that the patients received their dosage of the drugs every day. In an ordinary mass-treatment campaign, such detailed supervision would be absolutely impracticable. Capsules for treatment must be given under supervision. The people suffering from framboesia are of such a low educational standard that they cannot be trusted to take the capsules home with them and to take them regularly as instructed. Supervision of the taking of the capsules requires one of two things : either the patient must come in daily for a certain period to a central point where a supervisor such as a doctor, nurse, or sanitary inspector can give out the capsules; or else the supervisor must visit the homes of the patients. On a large-scale trial, both these are impracticable in the country, because the villages may be almost inaccessible or far from the medical centres.

As a result of our trials in Jamaica, involving the treatment of about 200 cases by oral administration of aureomycin, chloramphenicol, and terramycin, we have come to the conclusion that the ideal treatment is a course of two intramuscular injections separated by an interval of a few days.

The price of the oral antibiotics is still very high, and the cost of treatment varies : 30-60 shillings ($4.2-$8.4), depending on the weight of the patient.

The arsenical and bismuth preparations, penicillin, aureomycin, chloramphenicol, and terramycin all appear to be equally efficacious in the treatment of framboesia, although various authors claim that some are better than others. The arsenical and bismuth preparations are not without their toxic manifestations, whereas the antibiotics are relatively non-toxic.

For ease of administration and supervision in mass treatment, it is believed that the " two-shot " treatment of penicillin far surpasses the giving of arsenic, bismuth, or the oral antibiotics, aureomycin, chloramphenicol, and terramycin. This may be summarized in tabular form as follows :

	Ideal treatment	*Arsenic and bismuth*	*Penicillin*	*Aureomycin, chloramphenico and terramycin*
Efficacy	+	+	+	+
Toxicity	0	+	0	0
Ease of administration	+	0	+	+
Ease of supervision	+	0	+	0
Low cost	+	+	+	0

If it were possible to produce repository antibiotics other than penicillin, then the claims of these antibiotics for use in the treatment of yaws would be much stronger.

However, it behoves us not to be too enthusiastic at this stage, and we must be wary of our claims for the antibiotics; it is salutary to read an extract from a paper given by Dr. Gideon of Jamaica to the West Indian Medical Conference in 1921. He said: " In Jamaica an intensive campaign has been and is being waged against this loathsome disease, and the almost miraculous cure of the condition by one or two injections of the Salvarsan preparations has, I fear, given us a false sense of security, for, notwithstanding the undoubted lesser incidence of the disease consequent on the active war being waged against it, one finds that many cases of reinfection occur after apparent cure has been effected".

ACKNOWLEDGEMENTS

The author wishes to acknowledge the help given by Lederle Laboratories Division, New York, the research grant given by them, and the supplies of aureomycin and aureomycin dressing (Davis & Geck, Inc.) made available by their local agents in Jamaica, H. D. Hopwood & Co., Ltd. He also wishes to thank Levy Brothers Ltd, local agents for Parke, Davis & Co., Detroit, for supplies of Chloromycetin (chloramphenicol) ; and Commodity Service Co., local agents for Pfizer Laboratories, New York, for supplies of terramycin.

Fig. 1, 2, and 3 are reproduced by kind permission of the editors of the *Annals of the New York Academy of Sciences.*

SUMMARY

In a brief introduction, it is pointed out that three antibiotics have been isolated since 1947 : chloramphenicol, aureomycin, and terramycin. Although certain differences exist between them, they have many characteristics in common : all three have a low degree of toxicity, and all three at proper dosage levels are equally effective

RÉSUMÉ

Dans une brève introduction, l'auteur signale que trois nouveaux antibiotiques ont été isolés depuis 1947 : le chloramphénicol, l'auréomycine et la terramycine. Malgré certaines différences, ces produits présentent de nombreux caractères communs ; tous trois n'ont qu'une faible toxicité et tous trois sont, à dose appro-

in certain diseases of man. Clinically, the difference is that one is more effective than another against a particular disease.

The pattern of resistance to these antibiotics is of the penicillin type rather than of the streptomycin type. They are therefore unlikely to produce a resistant type of organism in the human body.

For the author's own experiments on yaws in Jamaica, with oral administration of all three drugs, an approximate dosage estimate was made of 25 mg per kg of body-weight. In practice, this worked out at four capsules (1 g) per day for 14 days for adults, two capsules (0.5 g) daily for 14 days for children of 5-10 years of age, and one capsule (0.25 g) daily for 14 days for children under 5 years.

The author then considers the use of each antibiotic separately. A table shows the dosages used and results obtained with aureomycin by various authors in West Africa, Haiti, and Jamaica. Clinical cures were obtained in the greater number of cases, but healing of lesions was generally slower than with penicillin. No symptoms of toxicity, other than occasional nausea and vomiting, were observed. The author also gives a number of case-histories of failures and reinfections.

For chloramphenicol also, the dosages and the results obtained by authors in West Africa, South America, and Jamaica are tabulated. Occasional vomiting, nausea, and thirst were the only signs of toxicity noted. Case-histories are again given illustrating failure, relapse, or reinfection. The author notes that the healing of framboesial lesions was similar to that following treatment with aureomycin.

priée, également efficaces pour le traitement de certaines maladies de l'homme. Du point de vue clinique, les différences portent sur l'efficacité plus ou moins grande de tel antibiotique par rapport aux autres pour combattre une maladie donnée.

La résistance des bactéries à ces antibiotiques est comparable à celle qui a été observée avec la pénicilline plutôt qu'à celle que provoque l'emploi de la streptomycine; il est donc très peu probable que ces antibiotiques déterminent l'apparition dans le corps humain d'un type de germes résistant à leur action.

Dans les expériences qu'il a effectuées à la Jamaïque sur des cas de pian, l'auteur a adopté une posologie d'environ 25 mg d'antibiotique par kg de poids du corps, les trois médicaments étant administrés par voie buccale. En pratique, la dose a été de 4 capsules (1 g) par jour pendant 14 jours pour les adultes, de 2 capsules (0,5 g) par jour pendant 14 jours pour les enfants de 5 à 10 ans, et d'une capsule (0,25 g) par jour pendant 14 jours pour les enfants de moins de 5 ans.

L'auteur examine ensuite séparément le mode d'emploi de chaque antibiotique. Un tableau indique les doses d'auréomycine utilisées et les résultats obtenus par divers chercheurs en Afrique-Occidentale, à Haïti et à la Jamaïque. Le plus souvent, des guérisons cliniques ont été enregistrées, mais la cicatrisation des lésions a été en général plus lente qu'avec la pénicilline. Abstraction faite de nausées et de vomissements occasionnels, on n'a observé aucun symptôme d'intoxication. L'auteur décrit un certain nombre d'observations d'échecs et de réinfections.

Pour le chloramphénicol également, la posologie et les résultats obtenus par différents chercheurs en Afrique-Occidentale, en Amérique du Sud et à la Jamaïque sont présentés sous forme de tableau. Les seuls effets toxiques constatés ont été parfois des vomissements, des nausées et une sensation de soif. A cet égard encore, l'auteur décrit un certain nombre d'observations d'échecs, de rechutes ou de réinfections. Il note que la cicatrisation des lésions pianiques s'est opérée comme dans le traitement à l'auréomycine.

As regards terramycin, other authors are cited to show that it is close to penicillin in its curative effects, causing rapid disappearance of treponemes, cicatrization of the lesions, and sterilization of blood and lymph-nodes. A table showing dosages and results with this drug in Brazil, Haiti, West Africa, and Jamaica again indicates clinical cure in most cases. In a number of cases, the treponemes disappeared from primary lesions in 24-36 hours and there was healing within four days. In Haiti, out of 150 cases treated, vomiting, nausea, and anorexia were noted in five ; in Jamaica, all 8 patients treated complained of intense thirst.

It is shown that the patterns of the serological results following treatment with aureomycin and chloramphenicol are very similar ; of 41 cases in Jamaica treated with the former and 81 cases with the latter, 78% and 80%, respectively, showed a fall in titre almost approaching seronegativity, while 18% and 10%, respectively, showed no fall. Of all 122 cases, 12% showed a rise in titre two weeks after treatment, with a subsequent decrease.

In the final section, the author states that, while oral therapy would seem ideal for administration, children find it very difficult to swallow the capsules, and that it is difficult to supervise the taking of capsules daily for 14 days. Close supervision was possible in Jamaica, but it required a special effort which would not be practicable in a mass campaign. The author concludes, from his own experience, that two intramuscular injections given at a few days' interval would constitute the ideal treatment and that, were it possible to produce aureomycin, chloramphenicol, and terramycin in repository form, as has been done with penicillin, their claims

En ce qui concerne la terramycine, l'auteur cite plusieurs autres chercheurs afin de montrer que les effets curatifs de cet antibiotique sont presque identiques à ceux de la pénicilline : disparition rapide des tréponèmes, cicatrisation des lésions et stérilisation du sang et des ganglions lymphatiques. Un tableau indique la posologie et les résultats obtenus avec ce médicament au Brésil, à Haïti, en Afrique-Occidentale et à la Jamaïque ; ici encore, on a constaté une guérison clinique dans la plupart des cas. Dans un certain nombre de cas, on a observé la disparition des tréponèmes dans les lésions primaires en 24 à 36 heures et la cicatrisation dans les quatre jours. A Haïti, sur 150 cas traités, on a enregistré cinq cas de vomissements, de nausées et d'anorexie ; à la Jamaïque, les 8 malades traités se sont tous plaints d'une soif intense.

L'auteur montre qu'à tout prendre les résultats sérologiques obtenus par le traitement à l'auréomycine, d'une part, au chloramphénicol, d'autre part, présentent une grande analogie : à la Jamaïque, sur 41 cas traités à l'auréomycine, on a noté une baisse du titre voisine de la séronégativité chez 78% des malades et l'on n'en a constaté aucune chez 18% des sujets ; les chiffres correspondants enregistrés après traitement de 81 cas par le chloramphénicol ont été de 80% et de 10% respectivement. Sur l'ensemble des 122 cas, 12% ont présenté, deux semaines après le traitement, une élévation du titre suivie d'un fléchissement.

Dans la dernière partie de l'article, l'auteur observe que si l'administration par voie buccale pouvait sembler le mode idéal de traitement, les enfants éprouvent toutefois de grandes difficultés à avaler les capsules et qu'il est difficile de surveiller pendant 14 jours l'ingestion quotidienne du médicament ingéré sous cette forme. A la Jamaïque, il a été possible d'exercer une surveillance rigoureuse mais au prix d'efforts particuliers que l'on ne saurait pratiquement envisager lors d'une campagne systématique. Se fondant sur sa propre expérience, l'auteur conclut que deux injections administrées par voie intramusculaire à quelques jours d'intervalle

to be used in treating yaws would be much stronger.

constituent le traitement de choix; s'il était possible — ajoute-t-il — de fabriquer des préparations-retard d'auréomycine, de chloramphénicol et de terramycine, comme on a pu le faire pour la pénicilline, l'emploi de ces antibiotiques dans le traitement du pian serait beaucoup plus recommandé.

BIBLIOGRAPHY

1. Ampofo, O. & Findlay, G. M. (1950) *Nature, Lond.* **165**, 398
2. Ampofo, O. & Findlay, G. M. (1950) *Trans. R. Soc. trop. Med. Hyg.* **44**, 311
3. Ampofo, O. & Findlay, G. M. (1950) *Trans. R. Soc. trop. Med. Hyg.* **44**, 315
4. Ampofo, O. & Findlay, G. M. (1951) *Trans. R. Soc. trop. Med. Hyg.* **45**, 261
5. Bryson, V. & Demerec, M. (1950) *Ann. N.Y. Acad. Sci.* **53**, 283
6. Chambers, H. D. (1938) *Yaws (framboesia tropica)*, London
7. Cunha, A. M. da, Area Leao, A. E., Guimarães, F. Nery & Cardosa, H. T. (1944) *Mem. Inst. Osw. Cruz* **40**, 195
8. Demerec, M. (1949) *J. clin. Invest.* **28**, 891
9. Demerec, M. & Demerec, R. (1950) *Bact. Proc.*, p. 101
10. Duggar, B. M. (1948) *Ann. N.Y. Acad. Sci.* **51**, 177
11. Dwinelle, J. H., Sheldon, A. J., Rein, C. R. & Sternberg, T. H. (1949) *Amer. J. trop. Med.* **27**, 633
12. Eagle, H., Magnuson, H. J. & Fleischman, R. (1946) *Johns Hopk. Hosp. Bull.* **79**, 168
13. Ehrlich, J., Batrz, Q. R., Smith, R. M. & Joslyn, D. A. (1947) *Science* **106**, 417
14. Findlay, G. M., Hill, K. R. & MacPherson, A. (1944) *Nature, Lond.* **154**, 795
15. Finlay, A. C., Hobby, G. L., P'an, S. Y., Regna, P. P., Routien, J. B., Seeley, D. B., Shull, G. M., Sobin, B. A., Solomons, I. A., Vinson, J. W. & Kane, J. H. (1950) *Science*, **111**, 85
16. Guimarães, F. Nery & Travassos, J. (1950) *Hospital, Rio de J.* **38**, 295
17. Hendricks, F. D., Greaves, A. B., Olansky, S., Taggart, S. R., Lewis, C. N., Landmein, G. S., MacDonald, G. R. & Welch, H. (1950) *J. Amer. med. Ass.* **143**, 4
18. Hill, K. R. (1951) *W. Indian med. J.* **1**, 81
19. Hill, K. R., Findlay, G. M. & MacPherson, A. (1946) *Lancet*, **2**, 522
20. Hill, K. R., Rhodes, K., Escoffery, G. S. & Murray, C. C. (1951) *W. Indian med. J.* **1**, 93
21. Levaditi, C. & Vaisman, A. (1951) *Pr. méd.* **59**, 849
22. Lins, S. A., Guimarães, F. Nery, Vasconcellos, P. & Miranda, J. L. (1950) *Rev. brasil. Med.* **7**, 439
23. Loughlin, E. H. & Joseph, A. A. (1951) *Antibiot. and Chemother.* **1**, 76
24. Loughlin, E. H., Joseph, A. A. & Schaeffer, K. (1951) *Amer. J. trop. Med.* **31**, 20
25. Logfren, R. C. (1944) *Nav. med. Bull., Wash.* **43**, 1025
26. O'Leary, P. A., Kierland, R. R. & Herrell, W. E. (1948) *Proc. Mayo Clin.* **23**, 574
27. Payne, E. H., Bellerive, A. & Jean, L. (1951) *Antibiot. and Chemother.* **1**, 88
28. Reynolds, F. W., Guthe, T. & Samame, G. (1951) *J. vener. Dis. Inform.* **32**, 236
29. Robinson, R. C. V., Fox, L. M. & Duvall, R. C. (1949) *Amer. J. Syph.* **33**, 509
30. Rodriquez, J., Plotke, F., Weinstein, S. & Harris, W. W. (1949) *J. Amer. med. Ass.* **141**, 771
31. Romansky, M. J., Olansky, S., Taggart, S. R. & Robin, E. D. (1949) *Science*, **110**, 639
32. Saunders, G. M., Chambers, H. D. & Rerrie, J. I. (1936) *Annual report of the Jamaica Yaws Commission for 1936*, Kingston, Jamaica

33. Schaeffer, K., Loughlin, E. H. & Joseph, A. A. (1951) *Amer. J. trop. Med.* **31**, 24
34. Schoch, A. G. & Alexander, L. J. (1950) *Ann. N.Y. Acad. Sci.* **53**, 549
35. Thomas, E. W. (1949) *Syphilis : its course and management*, New York
36. Welch, H. (1950) *Ann. N.Y. Acad. Sci.* **53**, 253
37. Whitehill, R. & Austrian, R. (1944) *Johns Hopk. Hosp. Bull.* **75**, 232