Opportunities for Research Work

Let me now make brief reference to the important part in promoting this growth and integration of scientific activities in medical research played by the great changes which have occurred in the source and the scale of the material provision available for its support. Those of us who wished to try our hands at research in the medical field at the opening of the century competed hopefully for the rare crumbs of brief opportunity, which then fell infrequently from a few small private endowments. You know how profoundly that position has been altered. With much larger funds available from private generosity, and with even more important and steadily expanding grants of public money, administered by the Medical Research Council or dispensed through the University Grants Committee, no man with a genuine impulse and with an adequate equipment of training and temperament for medical research need fail now to find an opportunity to prove his aptitude, and, if the result be favourable, to give medical research then at least a prominent place in his life's plans and ambitions. I am one of a great number who have reason to be grateful for the opportunities which have been created under this new dispensation.

There have been and may still be some, however, who, while they would acknowledge that the results, so far, appear to have been broadly beneficial, are doubtful and suspicious concerning the ultimate effects of this predominant support from public funds on the freedom of medical research, and therewith on its long-range effectiveness, as well as on its scientific spirit. Up to a point I can understand this anxiety, considering what might happen under an administration less wise and sympathetic, less expert and independent, than that which has hitherto been responsible for the effective decisions.

The anxiety in question is not unconnected, I think, with a more general discussion, now current, of the proper aim of research in all departments of science. You will no doubt have heard it argued by some that the proper aim of research is to discover truth for its own sake, and by others that it is to discover means for the material improvement of the lot of mankind. If you follow the arguments in detail, however, you will find that those who advocate the pursuit of knowledge for its own beauty and excellence often support their claim by evidence that this has led to the widest and most beneficent of practical developments; while those who insist that material benefit is the proper aim justify encouragement of the most abstract researches as an eventual contribution to that practical end. One begins to wonder, indeed, whether there is much to choose between these rival creeds. It has to be remembered however, that the advocacy of material human benefit, as the only acceptable aim, has associations with a particular political philosophy, and thus with plans for a central, authoritative direction of research. Theories, like people who seem innocent in themselves, may prove to be dangerous through the company they keep.

The Ultimate Aim

In dealing with medical research, in particular, material benefit to human life and health must surely be accepted as the ultimate aim; I can find no other meaning for the word "medical" in such a connexion. And our chief concern must be to ensure that the public funds directly granted for medical research continue to be administered and allotted, as hitherto, by a Council composed predominantly of experts who know the meaning of research, and who can be trusted to recognize the ways in which its truly

scientific pursuit can most effectively be encouraged, without either facile enthusiasm or obstinate caution. Such administrators will know from their own experience that, while the consciousness of the ultimately philanthropic purpose must be retained, and may even provide a valuable stimulus, success in medical research very often depends on an investigator's freedom to seize and to follow an unexpected clue, even when it appears to lead far from the original objective, and in a direction offering no visible likelihood of practical developments. They will be aware of the danger of short cuts, taken in the hope of reaching some dramatically practical result, without submission to the full and exacting discipline of science; and they will know how to hold and adjust the balance between the claims of researches undertaken to develop existing knowledge for medical uses and of those which plan bolder adventures into the unknown. While the administration remains safely under such expert and independent control, the support of medical research from the public funds, now an indispensable condition of its pursuit in this country on the present progressive scale, will continue to be protected from any serious danger to its freedom and integrity. Such danger could arise only if the distribution of the available funds were to become subject to political pressure, seeking to influence its direction in order to satisfy some popular clamour or sentiment, to meet some official convenience, or to enhance some Minister's prestige.

LABORATORY AND CLINICAL EXPERIENCE WITH TERRAMYCIN HYDROCHLORIDE

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A comparatively recent addition to the field of chemotherapy is the new antibiotic "terramycin hydrochloride," first reported in America by Finlay *et al.* (1950). This substance was obtained as a pure amphoteric compound from the growth of a soil actinomycete, *Streptomyces rimosus*.

There is already an extensive American literature, and much is in course of publication, on the physical, chemical, bacteriological, and clinical properties of terramycin (Finlay *et al.*, 1950; Hobby *et al.*, 1950; Welch *et al.*, 1950; Herrell *et al.*, 1950; Bliss *et al.*, 1950).

Terramycin hydrochloride is a sulphur-coloured compound with a bitter taste. It is sparingly soluble in water at pH 7, but can be readily dissolved by the addition of NaOH to pH 8.3-8.5, forming the sodium salt, or by adding HCl to lower the pH to 2, when the hydrochloride becomes soluble.

Stability

In contrast to "aureomycin," terramycin is a relatively stable antibiotic in solution. We have found that the acid solution at pH 2 maintains its potency for up to 30 days when kept at 0° C. as judged by assay against a standard staphylococcus. The alkaline solution maintains its potency for about seven days at 0° C., but it slowly deteriorates thereafter, turning dark brown in colour, and forms a

precipitate due to hydrolysis. This precipitate when redissolved still possesses considerable activity.

The stability of the hydrochloride in human serum was found to parallel closely that of the aqueous solution. The terramycin level in sera kept at 0°C. showed no appreciable fall in seven days. The effect of heat is shown in Fig. 1. A temperature of 100°C. is necessary to

FIG. 1.—Effect of heat on solutions of terramycin of strength 160 µg./ml. at pH 7.

inactivate completely a terramycin solution of 160 µg./ml. in 60 minutes at pH 7, there being little deterioration in 10 minutes at 80°C. The latter temperature and time suffice to sterilize contaminated fluids such as urine prior to assaying its antibiotic content. A lower concentration of 16 µg./ml. was completely inactivated in 30 minutes at 100°C. The relatively stable character of terramycin hydrochloride solution makes it a much more satisfactory antibiotic than aureomycin from the point of view of the laboratory worker.

Laboratory Assay

The standard techniques for the assay of other antibiotics have been tried with equal success for terramycin hydrochloride. In practice an inoculum of 10 c.mm. of an overnight broth culture of the Oxford staphylococcus to 10 ml. of digest broth was used to assay the antibiotic in aqueous solution, serum, urine, or filtrates of faeces. The microcapillary technique of Fleming and Smith (1947), while very convenient, was found to give growth at slightly lower dilutions than with the tube dilution method which was used as a routine. The familiar "filter-paper disk," "cork-borer hole," and "ditch" techniques applied to other antibiotics can also be used for rough sensitivity tests with terramycin. In practice the organisms isolated from patients treated with the antibiotic were all assayed by the serial dilution method in broth and read at 24 hours to give as accurate a picture as possible of their sensitivity and to observe any development of resistance. The standard solutions of terramycin hydrochloride used in these series of investigations were all prepared at strengths of the order of 2,500 µg./ml. and dissolved in dilute HCl at pH 2 and kept frozen solid. Dilutions for assay were made from these stronger stock solutions and were replaced approximately every three weeks. This has been found to be more satisfactory than using the less stable though highly soluble alkaline solution at pH 8.5.

Blood serum levels were assayed using the Oxford staphylococcus in tubes in broth as mentioned above;

urine was first diluted 1 in 10 and then used similarly. Faeces concentrations were estimated after emulsifying 1 g. in 10 ml. of distilled water, centrifuging, and heating the supernatant at 80°C. for 10 minutes for sterilization.

Bacterial "Spectrum"

As with chloramphenicol and aureomycin, terramycin hydrochloride is a "broad-spectrum" antibiotic. Table I shows the range of sensitivity of some of the commoner

TABLE I.—Sensitivity of Some Commoner Micro-organisms to Terramycin Hydrochloride

	Lowest inhibiting Concentration (µg./ml.)
<i>Staph. aureus</i>	0.25
Haemolytic streptococcus Group A	0.125-0.25
" B	0.5
<i>Str. pneumoniae</i>	0.25
" <i>faecalis</i>	0.5
" <i>viridans</i>	0.25
<i>C. diphtheriae</i> (mitis)	0.25
<i>Cl. welchii</i>	0.5
<i>N. gonorrhoeae</i>	0.25
<i>Bact. coli</i>	1.0-20.0
" <i>friedländeri</i> (Kl. 41)	1.25
<i>H. influenzae</i>	3.0
<i>Salm. typhi</i>	5.0
" <i>typhi-murium</i>	1.0
<i>Sh. flexneri</i>	1.0
<i>Pr. vulgaris</i>	200+
<i>Ps. pyocyanea</i>	5.0-200
<i>B. anthracis</i>	0.25
" <i>subtilis</i>	0.25
" <i>cereus</i>	0.25
<i>M. tuberculosis</i> H37Rv†	12.5
" <i>phlei</i>	4.0

* Mutant resistant to 500+ µg. of streptomycin per ml.
† Ten days' incubation, Dubos medium at 37°C.

micro-organisms so far tested. It will be seen that the antibacterial activity follows aureomycin closely. In general it is highly active against Gram-positive cocci and Gram-negative cocci. The intestinal group of Gram-negative bacilli are usually sensitive to concentrations below 10 µg./ml., with the exception of *Proteus vulgaris* and some strains of *Pseudomonas pyocyanea*. However, most strains of *Ps. pyocyanea* have been found to be relatively sensitive to concentrations as low as 5-15 µg./ml. (Of a total of 35 strains tested, 24 were sensitive to concentrations below 15 µg./ml.)

American investigators (Hobby *et al.*, 1950; Snyder *et al.*, 1950) report marked activity against the brucella and rickettsia. It is also reported to have a highly potent *in vitro* effect against *Entamoeba histolytica* (Most *et al.*, 1950), but little or no activity against viruses (Quilligan *et al.*, 1950).

Development of Bacterial Resistance.—During the treatment of the cases described, no resistant mutants of originally sensitive strains have appeared; particular attention in this respect has been paid to strains of coliform bacilli in urinary infections. *In vitro* experiments indicate that with some coliform strains a slow step-like resistance can be evoked, but there has so far been no occurrence of any "streptomycin-like" resistance.

Toxicity.—American reports (Pan *et al.*, 1950) show that the LD50 doses of terramycin hydrochloride for mice are 140 mg. per kg. intravenously and 2,240 mg. per kg. orally. This suggests that its behaviour in this respect is very similar to that of aureomycin, the corresponding figures of which are 134 mg. per kg. intravenously and 2,500+ mg. per kg. orally (Harned *et al.*, 1950).

Experimental Administration

Intravenous administration of terramycin in saline was undertaken, a rabbit of 2,400 g. weight being used. Fig. 2 shows the results of periodic serum and urine assay following a dose of 40 mg. per kg. body weight. This was the largest dose used during these investigations, and it gave rise to

slight incoordination and twitching, coming on two minutes after injection; these signs lasted about one minute. These symptoms may well have been due to the use of an

FIG. 2.—Results of intravenous injection of rabbit with 40 mg. of terramycin hydrochloride per kg. body weight (total 100 mg.).

unbuffered solution. There were no side-effects observed when smaller doses of the order of 20 mg. per kg. body weight were given intravenously to the same animal.

Administration of Single Doses to Man

The response of human volunteers to oral administration varied. Fig. 3 shows the average serum level obtained after a single dose of 250 mg. to healthy young males and the average response to a single dose of 1,000 mg.

It had been noted previously (Herrell *et al.*, 1950) that the levels of terramycin obtained in blood and urine bore little apparent relation to the dose ingested, though on the whole the higher doses resulted in the production of higher levels. These observations were usually concerned with single-dose administration, though some of them recorded multiple-dose levels.

FIG. 3.—Responses to single oral doses of terramycin hydrochloride. Each point is average of four investigations.

Early experiments showed that urine and serum levels tended to rise for the first 24 hours on six-hourly dosage, but thereafter rose no further. We accordingly determined serum and urine levels, after the first 24 hours, on 27 patients who were having courses of terramycin lasting from 5 to 10 days (Table II).

TABLE II.—Showing Oral Dosage and Concentrations Attained in Serum and Urine of 27 Patients (µg./ml.)

Dose mg./kg.	No. of Cases	No. of Serum and Urine Observations	Average Serum Level	Range Average Serum Level	Average Urine Level	Range Average Urine Level	Ratio Urine/Serum
0-10	1	2	0	—	25	—	—
10-20	1	4	0	—	100	—	—
20-30	Nil	—	—	—	—	—	—
30-40	2	8	1-25	0-2-5	100	50-150	—
40-50	4	30	5-7	3-5-8-7	165	100-325	29
50-60	1	2	10-0	—	260	—	26
60-70	4	18	7-7	4-5-10-0	205	120-250	27
70-80	6	20	6-8	5-0-9-0	230	120-500	34
80-90	4	16	8-1	3-5-10-0	240	100-400	29
90-100	4	16	6-9	5-0-11-25	490	250-750	71

Several sets of observations were made with samples of serum taken at various times during a single-dose period—that is, usually six hours—and these, though showing some variation, maintained a moderately stable level. It was concluded from these findings and our earlier experimental observations that, except perhaps for ease of administration, dosage need not be more frequent than six-hourly.

Doses were calculated on a basis of mg. terramycin per kg. body weight. Analysis of the original data showed that on a particular dose schedule some persons maintained higher blood and urine concentrations than others; it was noted that a high blood concentration usually ran *pari passu* with a high urine concentration. It has not yet been possible to relate these differences to increase or decrease of faecal excretion, as our data on this point are incomplete.

To compensate for the different number of estimations on serum and urine in individual patients, the figures for each patient were averaged before incorporation in Table II. This table shows the average and the range of the serum and urine levels obtained at various dose levels. Figs. 4 and 5 show the average of the serum and urine concentration for each case plotted against dose, with the average put in at each 10 mg. per kg. step. The wide variations in the levels are well seen from these graphs, but they also illustrate that, with a sufficient number of cases, levels tend to rise progressively with the dose.

The sharp rise in urine values and the urine/serum ratio at the highest-dose level is of considerable interest, and seems to indicate that, if absorption from the gut increases with greater doses, higher blood levels will not be reached owing to spill-over into the urine. This suggestion gains weight from the fact that, though we have on occasion administered high doses experimentally, we have never recorded a serum level greater than 12.5 µg./ml., though this level has been reached several times.

These dose curves suggest that even for severe infections a total dosage of 70 mg. per kg. daily at six-hourly intervals will give maximal blood levels, while numerous patients will attain such levels on about 50 mg. per kg. daily; lower dosage than these would need control by blood-level determinations.

The study of the urine levels related to dosage shows that terramycin is excreted in high concentrations and that adequate levels can be attained on very small dosage. As will be seen from the earlier data and, later, from the clinical section, most of the common urinary pathogens are susceptible to less than 10 µg./ml.; no dose that we have

yet administered has given levels as low as this. Certainly it would seem from these data that 50 mg. per kg. daily would be more than an adequate dose for most urinary infections, and half this dosage would probably be satisfactory. It is, however, one thing to consider this question

FIG. 4.—Relation between serum level and dose (oral). + Average serum levels for each case. —○— Average serum level as calculated from Table II.

FIG. 5.—Relation between urine level and dose (mg./kg. body weight). + Average urine levels for each case. —○— Average urine levels as calculated from Table II. —□— Ratio urine/serum $\times 10$ as calculated from Table II.

from an *in vitro* angle and quite another to deal with an infection *in vivo*, and we should like to emphasize at this stage that our clinical experience has been mostly with 50 mg. per kg. or greater.

Passage through Serous Membranes

Our experience of terramycin levels other than in the serum, urine, and faeces has been small, but in view of the comparatively recent discovery of the drug the following incomplete data may be of interest.

In one case of Reiter's syndrome with effusion into a joint, after 48 hours' treatment analysis of the joint fluid showed 2.5 $\mu\text{g.}$ of terramycin per ml., the serum level being 5 $\mu\text{g./ml.}$ In one case of pleural effusion after 24 hours' terramycin administration the pleural fluid level was

2.5 $\mu\text{g./ml.}$, whilst the serum level was 5 $\mu\text{g./ml.}$ One case with a biliary fistula showed a very high level (50 $\mu\text{g./ml.}$) in the bile with quite moderate serum levels.

American experience indicates that terramycin passes into the cerebrospinal fluid in low concentration only, at least in normal persons. It seemed to us that a more useful approach might be to test the passage of terramycin into abnormal meninges, since the intrathecal passage of the drug would be only of therapeutic interest in such persons.

We accordingly selected six cases suffering from tuberculous meningitis; these cases would have abnormal meninges, and we were in addition interested to see whether bacteriostatic concentrations to the tubercle bacillus (probably 10–20 $\mu\text{g./ml.}$) could be produced in the theca.

Owing to the fact that these cases were having streptomycin and it was not possible to stop this during the experiment, we had to use a highly streptomycin-resistant but terramycin-sensitive *Bact. coli* as the test organism. Under such conditions it was not possible to detect the presence of less than 1 $\mu\text{g.}$ of terramycin per ml.

In all of these cases the meningitis had largely settled down. In no case after 24 hours, despite serum levels between 5 and 10 $\mu\text{g./ml.}$, was there a detectable C.S.F. level; and after 72 hours, during which these high serum levels were maintained, only three out of five cases had approximately 1 $\mu\text{g./ml.}$ present in the C.S.F.

Probably in bacterial meningitis these figures would be improved, but we have as yet no data to support this assumption.

Effect on Intestinal Flora and Concentration in Faeces

The effect on the normal intestinal flora was investigated in eight cases receiving 1 g. of terramycin six-hourly. Specimens of faeces were examined the day before administration began, and daily specimens were examined during the four days in which the drug was ingested and after administration ceased.

After 24 hours' administration the colonies of coliform bacilli and faecal streptococci were diminished, and were eliminated entirely in all cases by the third day. The normal flora became replaced by a heavy growth of *Pr. vulgaris* in four cases, *Pr. morgani* in two, and in two a heavy growth of a yeast appeared; one of these also produced a few colonies of an atypical coliform which was found to be resistant to 200+ $\mu\text{g.}$ of terramycin per ml. Transient appearance of a few colonies of relatively resistant strains of *Ps. pyocyanea* was noted in two cases; these disappeared as administration proceeded. Our observations show that with three days' oral administration of terramycin complete alteration of the flora results. One case of ulcerative colitis produced a sterile specimen of faeces after three days' treatment.

Fourteen observations on the concentration of terramycin in the faeces were made on six cases receiving doses between 66 and 87 mg. per kg. daily. The results after the first 24 hours ranged from 500 $\mu\text{g./g.}$ faeces to as high as 4,000 $\mu\text{g./g.}$ Most of the estimations were grouped round 1,250 $\mu\text{g./g.}$ Such high concentrations as these fully explain the remarkable effects produced on the bacterial flora of the gut, since all gut organisms with the exception of various strains of *Proteus* are susceptible to concentrations many times less than those obtained (see Table I).

Faecal excretion does not tend to rise after the first 24–48 hours. Terramycin is usually present in the faeces in moderate concentration for one to two days after cessation of treatment. There was no appreciable absorption

from the rectum, since two trials of 2 g. administered rectally as a buffered solution at pH 8 in the form of sodium salt gave no detectable blood levels.

We cannot yet say whether this high faecal concentration is wholly the result of a proportion of the ingested dose being unabsorbed or whether some part of the terramycin is excreted into the gut by means of the bile or in other ways.

Clinical Experience

So far our clinical experience has been limited to the treatment of 29 cases; the results in four could not be assessed.

Urinary Infections

Thirteen cases of urinary infection have been treated; seven of these were uncomplicated by demonstrable anatomical abnormality of the urinary system, while the other six had complications such as hydronephrosis, vesical diverticulum, prostatic obstruction, or urethral stricture. Ten cases had been treated previously with sulphonamides or antibiotics, and the organisms all showed resistance to one or more chemotherapeutic agents. All cases were given doses at six-hourly intervals to a total amount of 50–80 mg. per kg. daily.

The pathogenic bacteria involved in the seven uncomplicated cases were either *Bact. coli* or *Str. faecalis*, or both. Sensitivity of these organisms ranged from 1 to 10 µg. of terramycin per ml.

All cases showed a rapid response, catheter samples being sterile at the end of either 24 or 48 hours; treatment was continued for at least 48 hours after the first sterile specimen, and no relapses have so far been seen. Constitutional symptoms were also rapidly controlled.

The results in all the cases with complicating mechanical factors show several features of interest. One case with unilateral hydronephrosis, urethral stricture, and diabetes showed a heavy urinary infection with *Bact. coli* and *Str. faecalis*. Numerous agents had been administered for the control of this infection without success; after one week's treatment these organisms disappeared, becoming replaced, however, by *Pr. vulgaris*. This occurrence did not interfere with the complete symptomatic relief afforded.

Two cases of post-prostatectomy infection and one of prostatic obstruction, all infected with *Ps. pyocyanea* and other organisms, were treated. The sensitivities of the strains of *Ps. pyocyanea* ranged from 3 to 10 µg. of terramycin per ml. All three cases showed very heavy infection; one case was cured after a week, one case responded rapidly but relapsed after treatment ceased, with the appearance of *Pr. vulgaris* and recurrence of *Ps. pyocyanea*. The third case responded rapidly until a resistant atypical coliform organism appeared for the first time, requiring chloramphenicol for its control. Unfortunately these cases were treated at a time when there was a temporary shortage of the drug; longer treatment with higher dosage would probably have been even more effective. Further work is in progress on the important question of *Ps. pyocyanea* infection, as, despite earlier American reports that most strains are resistant, nearly three-quarters of the strains isolated in these laboratories are sensitive to therapeutic concentrations of terramycin. Observations made upon urinary pH during treatment did not suggest that the control of this factor was of any great importance in producing cure.

Superficial Infections

A case of erythema multiforme bullosa with pyoderma showed a rapid response to treatment. This was a severe case in a frail old lady infected with *Staph. aureus*; *Bact.*

coli, and *Str. faecalis*. These organisms were inhibited by 0.5–5 µg. of terramycin per ml. but showed high resistance to all other antibiotics except aureomycin. A heavy nasal infection with *Staph. aureus* was also present. A course of 14 days' treatment was given; at the end of six days nasal swabs were sterile and skin swabs gave a very scanty growth of *Staph. aureus*. An immediate clinical effect was seen; the lesions dried and the heavy purulent discharge ceased, while skin-healing began and proceeded rapidly.

Another case of severe superficial sepsis was seen in the case of a girl of 12 who had had burns involving about one-third of the body surface two months previously. The child had experienced a very stormy illness, and long courses of penicillin, streptomycin, and chloramphenicol had failed to control the infection. Swabs showed *Staph. aureus* sensitive to 6 µg. of terramycin per ml. and *Ps. pyocyanea* sensitive to 15 µg./ml. After seven days' treatment *Ps. pyocyanea* had disappeared and only scanty colonies of *Staph. aureus* were seen. The appearance of the infected areas had undergone a complete change; the raw areas seemed healthy, the skin edges were advancing fast, discharge was minimal, and the patient's general condition had greatly improved. Skin-grafting was later possible.

A further case of *Ps. pyocyanea* infection was seen in a woman aged 23 suffering from spina bifida with neurological complications. Following pneumonia three months previously she had developed on each buttock a large indurated undermined ulcer which had defied all treatment. Swabs had always shown *Ps. pyocyanea*, and the sensitivity of this organism was 7 µg./ml. Under cover of systemic terramycin administration one ulcer was excised with success; the other healed under the influence of the drug.

A long-standing wound infection with *Ps. pyocyanea* (sensitivity 32 µg./ml.) was controlled by local application of a solution of strength 1,000 µg./ml., whilst a reasonable response was seen in the treatment by systemic means of a deep-seated ulcer with surrounding cellulitis situated in the natal cleft and infected with *Ps. pyocyanea* (sensitivity 15 µg./ml.) and *Bact. coli*.

Post-operative Infection

Four cases of post-operative complications were treated: one case of pneumonia with effusion following lobectomy for bronchiectasis (*Bact. friedländeri* and a pneumococcus), one of oesophageal abscess following oesphagoscopy (*Staph. aureus* and *Bact. coli*), one of post-operative peritonitis after hysterectomy (*Bact. coli* and *Str. faecalis*), and the last a case of pelvic cellulitis following vaginal hysterectomy (*Bact. coli*). All organisms were sensitive to less than 10 µg. of terramycin per ml.

The assessment of therapeutic effect on such cases is always difficult, as by the nature of the diseases other measures are employed concurrently. It can be said that all cases recovered completely, as fast as would be expected with the aid of efficient chemotherapy.

Miscellaneous Cases

Two patients with ulcerative colitis were treated. The first case, that of a man aged 39, had had long courses of streptomycin and chloramphenicol without benefit. A course of terramycin apparently produced great improvement, and he has remained well for three months after discharge.

The other case was not really suitable for assessment, as two months' hospital treatment had already caused a remission. Terramycin was administered in an attempt to clear his stools of blood, but without success.

One case each of dermatitis herpetiformis, Behcet's syndrome, and Reiter's syndrome, with arthritic involvement and joint effusion but with cessation of discharge, were treated with inconclusive or unsatisfactory results.

Toxic Symptoms

Of 33 patients who had courses of the drug lasting five or more days, 20 had no toxic symptoms. Thirteen patients, on direct questioning, admitted to feeling nauseated at times, usually at the beginning of the course; eight of these vomited one or more times. In the case of one very ill lady, vomiting was severe during the first 24 hours and the drug was stopped.

One case developed a sore throat, a severe substernal pressure sensation, and respiratory distress on the third day. The symptoms regressed 12 hours after the drug was stopped and further administration later did not reproduce this syndrome. No diagnosis was made of the cause of the symptoms, which may have been coincidental.

One old lady with very numerous disabilities developed an erythematous rash on the tenth day of treatment, and on the next day the Hess capillary test was very strongly positive. Two days later, while the normal faecal flora was still absent, the Hess test became normal. In her case all blood studies were normal; patch and prick tests to the drug were negative. Subsequently a further five-day course of terramycin was administered; the rash did not recur and the Hess test remained negative.

On the second and third days of treatment nine cases developed transient looseness of bowels; in three cases this was of moderate severity, but in none was it necessary to stop the drug.

In view of the profound changes in bacterial flora produced by the drug, a watch was kept for possible signs of vitamin deficiency: none was seen. It was felt that the case which developed the positive Hess test could not be regarded as one of vitamin deficiency, since the increased capillary fragility returned to normal whilst the usual bacterial flora of the bowel was still absent.

We noted that, as with aureomycin, the incidence of gastro-intestinal upset was greatly reduced by administering the drug with milk, and we were able to show that this procedure exerted no detectable effect upon the serum levels. It is perhaps of interest to state that with the one case in which the drug had to be discontinued owing to vomiting no milk was given.

Though the incidence of gastro-intestinal upset reported here is considerable, we used doses at the upper end of the scale, and with the exception of one case were able to continue with the drug. In three cases, however, in which vomiting occurred several times, very low serum and urine levels were recorded, which suggested that the oral route in these patients was unsatisfactory.

A suitable preparation of the drug for intravenous use has now been developed; this is claimed to be well tolerated and to circumvent gastro-intestinal symptoms in susceptible patients.

Conclusions

Our clinical experience has shown terramycin to be an antibiotic of low toxicity which is readily absorbed from the gut and which rises to satisfactory levels in serum, urine, faeces, and probably in most serous cavities. It is unfortunate that the blood-brain barrier is penetrated only poorly, but, as experience with other antibiotics has shown, this is not necessarily a bar to the efficient treatment of meningeal infections.

Our limited clinical results bear out expectations founded on the *in vitro* activity of the drug.

We would draw particular attention to the high levels of the drug in the urine and to our observations that the urinary pH seems to be immaterial in procuring successful results. The table of bacterial sensitivities shows that all the common urinary pathogens, with the exception of *Pr. vulgaris* and some strains of *Ps. pyocyanea*, are sensitive to concentrations many times less than those obtained therapeutically. It appears likely that with high dosage, leading to urinary levels of 300–400 µg./ml., practically all cases infected with *Ps. pyocyanea* will be amenable to therapy. Further, the fact that a number of strains of *Pr. vulgaris* are sensitive to chloramphenicol and streptomycin means that we now have efficient agents for the treatment of nearly all urinary bacterial infections.

In addition to our findings with the treatment of *Ps. pyocyanea* infections of the urinary tract, our preliminary data with regard to superficial infections with this organism show that terramycin offers real promise in controlling pyocyanea infections by local or systemic administration.

The striking changes in bacterial flora produced by terramycin and the high residual concentrations in the faeces will still further increase the scope and safety of gastro-intestinal surgery and enhance the medical management of intestinal infections.

We have noted in several cases that terramycin has produced clearing of abnormal nasal flora and considerable change in the bacterial content of sputum in cases of bronchiectasis; these findings indicate additional therapeutic uses.

We have not yet observed any striking difference in antibacterial activity between terramycin and aureomycin, with the one exception of *Ps. pyocyanea*, against which terramycin is more effective. Terramycin is also much more stable in solution than aureomycin, which is particularly advantageous in laboratory work.

We wish to express our grateful thanks to Professor Sir Alexander Fleming for much advice in these investigations and for enabling us to obtain supplies of terramycin, generously provided by Messrs. Chas. Pfizer and Co., of New York. We acknowledge the help and advice of Professor Robert Cruickshank and the valuable technical assistance of Mr. D. Stratful in the routine laboratory work. We also wish to thank the members of the consultant staff of St. Mary's Hospital for granting us access to the cases described.

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