carried out on patients with diseases other than active tuberculosis(5). We cannot explain the negative tuberculin skin tests reported in patients with active tuberculosis following the administration of ACTH(3,4).

The daily dose of ACTH or cortisone given to the animals in this experiment corresponds to 10.6 mg per kilo body weight. The morphologic changes in the adrenal cortex, the lymphoid tissue and other organs indicate the effectiveness of the injected hormones. Larger doses of cortisone gave similar results. In a different experiment positive tuberculin skin reactions were always present in 20 guinea pigs with active progressive tuberculosis which received daily 5 mg of cortisone for 50 days. In these animals the tuberculin skin reactions were obtained at 30 and 45 days after the beginning of hormone administration.

In our experiments ACTH or cortisone did not obliterate the tuberculin skin reaction but appeared to diminish its intensity. We believe that the hormones do not interfere primarily with the immune mechanism of the delayed type of antigen-antibody reaction. The apparent modification of the reaction might result from the inhibitory effect of adrenal corticosteroids on the acute inflammatory process(7).

*Summary.* Guinea pigs with active progressive tuberculosis were given ACTH or cortisone for 6 days. A definite tuberculin skin reaction was obtained in all animals during the period of hormone administration. The reaction appeared less marked in the treated animals than in the controls. It is suggested that ACTH or cortisone do not interfere primarily with the immune mechanism of the tuberculin skin reaction but decrease the associated acute inflammatory process.

7. Cummings, M. M., Michael, M., and Bloom, W. L., in press.

Received October 20, 1950. P.S.E.B.M., 1950, v75.

## The Relationship Between Aureomycin, Chloramphenicol, and Terramycin (18284)

FELIX E. PANSY, PAUL KHAN, JOSEPH F. PAGANO AND RICHARD DONOVICK

*From the Squibb Institute for Medical Research, New Brunswick, N. J.*

Herrell *et al.*(1), working with aureomycin, chloramphenicol and terramycin, found, for a number of strains of *Escherichia coli* and *Aerobacter aerogenes*, that when resistance developed against one of the 3 antibiotics there was a parallel increase in resistance to the other 2.

In the present study, strains of *E. coli* and *Micrococcus pyogenes* var. *aureus 209P* were made resistant to aureomycin or chloramphenicol by subjection to repeated increasing doses of the antibiotics. Their resistance to aureomycin, chloramphenicol and terramycin was then determined. The minimal inhibiting concentrations (M.I.C.) were determined in Difco Penassay Broth according to the method described earlier(2). The results obtained are presented in the accompanying table.

It will be noted that with both organisms, a rise in resistance to either aureomycin or chloramphenicol is accompanied by an increased resistance to the other 2 antibiotics. Thus, after 7 passages in the presence of chloramphenicol, *E. coli* D56 shows a 21-fold increase in resistance to this antibiotic, accompanied by an 11-fold increase towards aureomycin and a 6.5-fold increase to terramycin. After 8 passages in the presence of aureomycin-hydrochloride, a 31-fold increase in resistance is noted, accompanied by 27-fold and 12-fold increases in resistance to chloramphenicol and terramycin-hydrochloride, respectively. The case with *M. pyogenes* var. *aureus 209P* is much the same although re-

1. Herrell, W. E., Heilman, F. R., and Wellman, W. E., *Conference on Terramycin, Ann. N. Y. Acad. Sci.*, 1950, v53, 448.

2. Donovick, R., Hamre, D., Kavanagh, F., and Rake, G., *J. Bact.*, 1945, v50, 623.

TABLE I.

| Organism | Aureomycin HCl MIC in μg/ml | Chloramphenicol MIC in μg/ml | Terramycin HCl MIC in μg/ml |
|---|---|---|---|
| *Escherichia coli* D56 (Original strain) | 0.56 | 1.88 | 0.540 |
| *E. coli* D56 after 5 passages vs. chloramphenicol | 2.98 | 17.0 | — |
| *E. coli* D56 after 7 passages vs. chloramphenicol | 5.36 | 39.7 | 3.53 |
| *E. coli* D56 after 5 passages vs. aureomycin HCl | 2.51 | 5.23 | — |
| *E. coli* D56 after 8 passages vs. aureomycin HCl | 15.6 | 50.5 | 6.40 |
| *M. pyogenes* var. *aureus 209P* | 0.0507 | 1.85 | 0.122 |
| *M. pyogenes* var. *aureus 209P* after 9 passages vs. chloramphenicol | 0.116 | 5.57 | 0.186 |
| *M. pyogenes* var. *aureus 209P* after 10 passages vs. aureomycin HCl | 0.220 | 4.43 | 0.312 |

sistance develops more slowly.

A number of reports have appeared which suggest that an increase in resistance to an antibiotic may be paralleled by a rise in resistance to related antibiotics. Donovick and Rake(3) showed that 2 species of bacteria resistant to streptomycin were also resistant to dihydrostreptomycin. Rake *et al.*(4) found that when the resistance of a strain of *E. coli* was increased 25-fold for streptomycin there was a similar increase in resistance to mannosidostreptomycin. Further work(5) on the action of the streptomycins versus *Salmonella schottmülleri* has shown that when, by subjection to increasing doses of streptomycin, the organism's resistance is raised 22.6-fold, a parallel rise of 21.3-fold occurs for dihydrostreptomycin, 5.0-fold for mannosidostreptomycin, and 8.0-fold for dihydromannosidostreptomycin. Eisman, *et al.*(6) having made 2 strains of staphylococci resistant to penicillin G found similar rises in resistance to penicillins X and F. Dowling, *et al.*(7) found with various strains of pneumococci, streptococci, staphylococci, and meningococci made resistant to penicillins G and X, that organisms adapted to one penicillin similarly had acquired resistance to the others. Sullivan, *et al.*(8) worked with strains of *S. aureus* and *E. coli* made resistant to streptomycin, streptothricin and penicillin. The streptomycin and streptothricin used were crude extracts of cultures from *Streptomyces griseus* and *Streptomyces lavendulae*. They found that *E. coli* which had developed resistance to streptothricin was also more resistant to streptomycin. The reverse, however, was not true.

In so far as cross resistance to different antibiotics is concerned, the findings of Kelner and Morton(9) are difficult to interpret. These authors in describing the characteristics of lavendulin and actinorubin, noted that a 26,600-fold increase in resistance of *E. coli* P216, to streptomycin was accompanied by insignificant increases in resistance to lavendulin, actinorubin, and streptothricin. However, when the sensitive parent strain was made resistant to actinorubin by a factor of 64, it was also found to be 16 times more resistant to streptomycin, and 32 times as resistant to streptothricin and lavendulin. Similarly, when the sensitive parent strain was made resistant, by a factor of 32, to lavendulin, this organism had also become equally resistant to the 3 other antibiotics. Thus, while lavendulin and actinorubin had bacterial spectra different from each other, as well as different from those of streptomycin and streptothricin, yet under proper conditions, cross resistance appeared to occur. Since the purities of the various antibiotics used were not specified it is not possible to determine whether or not these cross resistances indicated similar modes

3. Donovick, R., and Rake, G., *J. Bact.*, 1947, v53, 205.

4. Rake, G., McKee, C. M., Pansy, F. E., and Donovick, R., PROC. SOC. EXP. BIOL. AND MED., 1947, v65, 107.

5. Pansy, F., Khan, P. and Donovick, R., to be published.

6. Eisman, P. C., Marsh, W. S., and Mayer, R. L., *Science*, 1946, v103, 673.

7. Dowling, H. F., Hirsh, H. L., and O'Neil, C. B., *J. Clin. Invest.*, 1946, v25, 665.

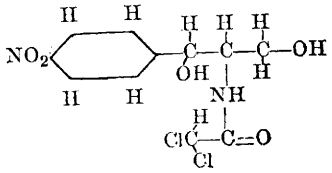
8. Sullivan, M., Stahly, G. L., Birkeland, J. M., and Myers, W. G., *Science*, 1946, v104, 397.

9. Kelner, A., and Morton, H. E., *J. Bact.*, 1947, v53, 695.

of action, or simply the presence of more than one antibiotic in the materials employed for developing the resistant strains. From the results obtained by Kelner and Morton(9), one might expect cross-resistance to develop against streptomycin and streptothricin, as had already been reported by Sullivan, *et al.* (8). However, Smith(10) has described a gram-negative organism which was resistant to 16,000 units of streptomycin per ml while it was inhibited by 7.5 units of streptothricin per ml. Hence, the picture on cross resistance, as far as these 2 antibiotics are concerned, is far from clear.

It would seem to be reasonable to assume that the occurrence of cross resistance of an organism between 2 antibiotics might well indicate that the 2 substances interfere with the same biological processes. This would not be surprising with the various penicillins or streptomycins. It would be more so in the case of streptomycin and streptothricin, but this observation remains somewhat in doubt. Therefore, the occurrence of cross resistance of organisms to chloramphenicol, aureomycin and terramycin is of particular interest. The chemistry of the first of these is completely known and has been described(11), but such is not the case with the latter two. Nevertheless, the empirical formulae of all three are known and indicate that the 3 antibiotics are distinct, one from the other, chemically(12-15).

Chloramphenicol $C_{11}H_{12}N_2O_5Cl_2$



Aureomycin $C_{23}H_{27}N_2O_9Cl$

Terramycin $C_{22}H_{24-26}N_2O_9$

Judging from the absorption spectra of aureomycin and terramycin, these 2 antibiotics must have much in common chemically. Their bacterial spectra are also similar.

Of great interest to the biologist would be the occurrence of cross resistance of an organism to compounds differing from each other fundamentally. This cannot be said to be the case, for example, where the streptomycins or the penicillins are involved. As already indicated, there is reason to believe that the case of cross resistance of organisms between streptomycin and streptothricin may be in doubt. Until complete descriptions of the molecular structures of aureomycin and terramycin become available, one cannot conclude the cross resistance shown to develop here for chloramphenicol, terramycin and aureomycin is an example of cross resistance to distinct chemical types of compounds.

*Summary.* *Escherichia coli D 56* and *Micrococcus pyogenes* var. *aureus 209P* on becoming resistant to aureomycin also become resistant at somewhat lower levels to chloramphenicol and terramycin. Similarly, on becoming resistant to chloramphenicol the two organisms become resistant at lower levels to aureomycin and terramycin.

10. Smith, D. G., PROC. SOC. EXP. BIOL. AND MED., 1946, v61, 214.

11. Controulis, J., Rebstock, M. C., and Crooks, H. M., Jr., *J. Am. Chem. Soc.*, 1949, v71, 2463.

12. Broschard, R. W., Dornbush, A. C., Gordon, S., Hutchings, B. L., Kohler, A. R., Krupka, G., Kushner, S., Lefemine, D. V., and Pidacks, C., *Science*, 1949, v109, 199.

13. Duggar, B. M., U. S. Patent 2,482,055 (September 13, 1949).

14. 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., and Kane, J. H., *Science*, 1950, v111, 85.

15. Regna, P. P. and Solomons, I. A., *Conference on Terramycin, Ann. N. Y. Acad. of Sciences*, 1950, v53, 229.

Received October 20, 1950. P.S.E.B.M., 1950, v75.