

U.S. GOVERNMENT MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
 FOOD AND DRUG ADMINISTRATION,
April 10, 1968.

To: Director, Bureau of Medicine.

From: W. B. Rankin, Deputy Commissioner.

Mr. Thomas Corcoran, an attorney representing Bristol Laboratories, presented the attached paper to Dr. William H. Stewart, acting for Dr. Philip Lee, on April 9.

Please let us have by close of business April 16, proposed comment from Dr. Goddard to Dr. Lee on this paper.

W. B. RANKIN.

Enclosure: Copy of paper.

The FDA has a theory (hereinafter called the reserve drug theory) that some antibiotics should be limited for use only in the treatment of resistant staphylococci infections even though some antibiotics are also concededly effective for the treatment of infections due to streptococci, pneumococci and non-resistant staphylococci. The FDA has implemented this theory by demanding that the labeling for these antibiotics (which are semi-synthetic penicillinase-resistant penicillins such as oxacillin, nafcillin, cloxacillin and most recently dicloxacillin which is awaiting FDA clearance) state in effect that if laboratory tests determine that the infection is caused by organisms that can be treated by the old line penicillin or by penicillin G, the physician must be advised to stop using the semi-synthetic penicillinase-resistant penicillin.

Curiously enough, the FDA forbids an explanation of this cryptic advice in the labeling. It is understood, however, that it is based on the possibility that some time in the future, there might appear in the environment organisms resistant to semi-synthetic penicillins if they are widely used now. Thus, semi-synthetic penicillins should be reserved for future use by implementing the reserve drug theory through labeling.

However, other antibiotics which have been marketed in the last few years have labeling which omits the elements of the reserve drug theory even though they are indicated also for use in the treatment of infections caused by pneumococci, streptococci and both resistant and non-resistant staphylococci. Such drugs include gentamycin, cephalothin, cephaloridine, methacycline, doxycycline and lincomycin. FDA approval of the omission is peculiar in view of the fact that resistant staphylococci strains have previously appeared shortly after market introduction of similar classes of antibiotics including many of the tetracyclines. Most recently, resistant staphylococci strains have appeared after lincomycin was marketed.

By comparison, although there are rare staphylococci in nature resistant to these penicillins, no significant increase in pathogenic strains which are resistant to the semi-synthetic penicillins have appeared even though methicillin has been in use over eight (8) years and oxacillin for over six (6) years. In contrast, strains resistant to penicillin and penicillin G appeared and increased shortly after those drugs were introduced. This omission, particularly with respect to the labeling for cephalothin and cephaloridine, is indefensible since these drugs are primarily used in hospitals where the problem of resistant infections developing is the most serious.

There are a number of explanations based on experience as to the reasons for the development of strains resistant to some antibiotics and not others. One turns on the distinction between bacteriostatic antibiotics (where resistant strains have usually developed) and bactericidal antibiotics (where resistant strains have not usually developed). It should be noted that such semi-synthetic penicillins as dicloxacillin are bactericidal rather than bacteriostatic, while many of the antibiotics not subject to the reserve drug theory are bacteriostatic.

These random applications of the FDA's policy become even less defensible when it is understood that the failure to apply the theory to the labeling of non-semi-synthetic-penicillin antibiotics would have a patient allergic to penicillin defenseless against some future epidemic of resistant staphylococci infection.

The scientific underpinnings of the reserve drug theory are extremely questionable. But unquestionably, its application has been discriminatory, arbitrary and scientifically unsound. Most recently, by applying the reserve drug theory to dicloxacillin, the FDA is in effect applying the test of relative efficacy in