II. *Expert opinions in resistance*

A. In the process of attempting to resolve the controversy regarding the labeling of dicloxacillin, the FDA, approximately one year ago, drafted and sent a questionnaire to eleven recognized experts in the field of microbiology and antimicrobial therapy. Among those questions asked, two deal directly with the immediate problem:

1. "Do you believe that penicillinase-resistant penicillins are now the drugs of choice for the routine treatment of all infections caused by gram-positive cocci susceptible to their actions?" All eleven experts answered "No."

2. "Assuming you have initiated chemotherapy with a penicillinase-resistant penicillin in a severe infection and the patient is showing excellent clinical response but the cultures now show the causative organism to be a Beta-hemolytic streptococcus or pneumococcus, would you change chemotherapy to penicillin G or V?" Eight answered, "Yes." Two answered, "No." One said, "Probably would not change."

B. Following the FDA poll, Bristol Laboratories drafted a set of questions dealing with the same problem and submitted them to a group of 15 physicians, some of whom are also regarded as experts in the field:

1. Included in Bristol's questionnaire was, "In your opinion should a penicillinase-resistant penicillin be reserved for the treatment of infections due to penicillinase-producing staphylocci when the penicillin has been shown to be highly effective both bacteriologically and clinically in infections due to streptococci and pneumococci?" Eleven answered "No." Two answered "Yes." One felt the question inappropriate, and one did not give a "Yes" or "No" answer.

2. Bristol did not include a question regarding the desirability of changing therapy to Penicillin G or V if culture subsequently showed the organism to be sensitive to Penicillin G or V.

C. On August 31, 1967 the FDA Medical Advisory Board was asked to consider this problem and give their recommendations. The Board was presented with the Bureau of Medicine position and the expert opinions as expressed in answers to all the questions in the FDA and Bristol questionnaires. After considerable discussion, the concern was expressed that the package labeling for these semisynthetic penicillins should limit their indications to thus permit observation whether staphylococcal resistance to these agents does become a significant problem. With this concern in mind the Board voted 4 to 2 to adopt the recommendation: "That the labeling for dicloxacillin contain 3 general statements:

"1. 'When the infecting organism is susceptible to Penicillin G the physician is advised to use penicillin G, V, or phenothicillin, because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.'

"2. 'The principle indication is in treating infections due to penicillinase producing staphylococci or in initiating therapy when there is the possibility of a resistant staphylococcic infection.'

"3. 'This product is also effective in treating infections due to streptococci, pneumococci, and penicillin sensitive staphylococci.' "

These recommendations were implemented by the Bureau of Medicine and equally applied in negotiating final labeling for all three dicloxacillin products (Wyeth, Ayerst, Bristol). The approach to labeling for dicloxacillin is well illustrated by the excerpt below:

The principal indication for sodium dicloxacillin monohydrate is in the treatment of infections due to penicillinase-producing staphylococci or in initiating treatment when there is the possibility of a resistant staphylococcic infection. Bacterilogoic studies should be performed. When the infecting organism is suspectible to penicillin G, the physician is advised to use penicillin G, V, phenothicillin or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

This product is also effective in treating infections caused by streptococci, pneumococci and penicillin-sensitive staphylococci.

III. *Comments on Bristol statement of March 28, 1968*

It is true, as Mr. Corcoran affirms, that the labeling advises the physician to use, or to change to, penicillin G when sensitivity studies indicate the pathogen is susceptible to it. It is not true (see the paragraph #1 above), as