twenty antibiotic agents had been described indicating this would be a fertile field for the discovery of agents beneficial in the treatment of disease. Already the ingenuity of the clinical investigators as well as the pharmaceutical industry was stimulated by speculation concerning the effect of various antibiotic combinations, particularly in connection with the agents in which they were individually involved. Dr. Welch specifically mentioned twelve combinations of antibiotics, a number of which fortunately have never found their way to the market place. No allusion was made to fixed combinations of antibiotics but these had already appeared and received the tacit approval of the Food and Drug Administration. This concept was further supported by the statement that there was "a distinct trend toward combined therapy, not an old fashioned 'shotgun' approach, but a calculated rational method of attacking the problem of resistant organisms". Despite this statement it was clear to many that the commonest purpose for the fixed combinations which were appearing was precisely that it was claimed not to be, namely, a shotgun approach to the treatment of undiagnosed disease. This was defined as a third era of antibiotic therapy, one in which combined therapy with combinations of chemotherapeutic agents, particularly synergistic ones, would be customarily used.

In response to this and at the same meeting a number of outstandingly competent physicians and clinical investigators in the field of infectious diseases spoke out politely but firmly both publicly and in private conversation with regard to the folly of this view. Notable among these were Drs. Maxwell Finland, Harry Dowling, and William Altemier. We are only today echoing the remarks of Dr. Harry Dowling recorded in the same publication as those of Dr. Henry Welch which were as follows:

"Therefore, one takes the chance in every case that (the bacteria causing an infection) is resistant to a certain antibiotic when he uses it. If he tests against two antibiotics and finds that the organism is sentitive to both, then he can get just as good a result wth one. Why use two? If he finds it is resistant to one and not to the other, then he is not going to get any effect by using the antibiotic to which it is resistant. Then we return to the fact that it may be sensitive to both. Is the patient any better off if we use two antibiotics? We may delay—and our work certainly does not show that we delay to any great extent—the appearance of resistant strains in these cases. Would the patient not be better off if we used good doses of one antibiotic and concentrated on that? If this fails, then we can use another antibiotic. We know exactly what we are doing. We know exactly where we are going and I doubt whether we do when we use more than one antibiotic." [2]

Further echoes are apparent in the remarks of Dr. William Altemier again at the same meeting:

"I feel it is very difficult and almost dangerous to practice medicine by generalities or by rules of thumb; that in infections of moderate severity produced by single species of bacteria, such as staphyloccocci, that one antibiotic should be used, and, wherever possible, it should be selected on the basis of the sensitivity results. Two should not be used in surgical infections under those circumstances, because if the surgical procedure necessary for the treatment of that case is timed in relation to the antibiotic therapy, the duration of that antibiotic therapy should be not longer than ten days and preferably usually five days, a period during which resistant strains are not apt to emerge and a period during which the infection is brought under control. I think the tendency to use two or more antibiotic agents in infections leads to procrastination in surgical infections, to delaying necessary operative procedures, and to an increased emergence of resistant strains." [3]

These principles, along with entreaties to the industry, were repeatedly stated for then to now,[4 5] but achieved comparatively low pitch in the next phase of development because of the economic rewards of pharmaceutical gimmickery and the tremendous impact of promotional activities by the industry. Two major broad-spectrum antibiotics, tetracycline and chloramphenicol, had become available by this time. Chloramphenicol was discovered, patented, and marketed solely

[2] Dowling, H., Susceptibility of Microorganisms to Antibiotics isolated from Hospitalized and Non-Hospitalized Persons (Panel Discussion), *Antibiotics Annual,* 1956–7, p. 1103, Medical Encyclopedia, New York, 1957.
[3] Alteimer, William, *Ibid.*, p. 1105.
[4] Dowling, H. F., Finland, M., Hamburger, M., Jawetz, E., Knight, V., Lepper, M. H., Mieklejohn, G., Rantz, L. A., and Rhoads, P. S., Clinical Use of Antibiotics in Combination. *Archives of Internal Medicine, 99:* 536, 1957.
[5] Edit., Antibiotic Combinations. *New England Journal of Medicine, 255:* 1057–9, 1956.