possible that certain combinations are synergistically toxic. Furthermore, if a patient on a drug combination does develop an untoward reaction, it is difficult and usually impossible to determine which one of the agents is responsible.

I have already spoken of the disadvantages of fixed drug combinations in terms of efficacy and potential toxicity. When the physician is dealing with fixed combinations, he will never find it possible to increase or lower the dose of one component of the mixture without at the same time affecting the dose of the other. In this circumstance, the tendency is either to raise the dose of one drug to a desired level and thus inadvertently to give an overdose of the other or to lower the dose of one compound and, consequently, give an insufficient dose of the other. All humans differ from each other, not only in such readily observable measurements as size, weights, and age, but also in terms of their ability to metabolize and excrete certain agents, their tendency toward the development of allergy, et cetera. The fixed combinations assume that everyone is the same, that an 80-year-old man differs little from a 20-year-old.

Furthermore, a number of the available combinations consist of agents which have either no usefulness, or limited usefulness combined with high toxicity, at least in the child population. A good example are the tetracycline-novobiocin combinations, Panalba and the tetracycline-oleandomycin combination, Signemycin. I might quote the overall evaluation of novobiocin prepared by my antibiotic panel of the National Research Council-National Academy of Sciences.

In summary, novobiocin is limited by (1) a narrow spectrum which duplicates that of many other agents, (2) rapid emergence of resistant strains, and (3) high frequency of adverse reactions, especially skin rashes and hepatic dysfunction. The development of safer and more effective drugs has virtually eliminated the need for novobiocin. The majority of the panel believes that orally administered novobiocin should be taken off the market.

Similarly, the panel's evaluation of triacetyl-oleandomycin and oleandomycin is as follows:

For each of the infections specifically mentioned in the package insert under "Indications" for which there are data to support chemotherapeutic activity, there are several antimicrobial drugs that the panel would recommend preferentially to triacetyl-oleandomycin (or oleandomycin).

It is dangerously misleading to list triacetyl-oleandomycin (or oleandomycin) without qualification as the drug to be used for any infection.

Furthermore, in a recent summary of the value of tetracyclines in pediatric practice, prepared at the request of the editors of The Journal of Pediatrics, my associates and I make the following statements:

The tetracyclines possess an unusually high index of toxicity, and a low order of activity against most of the organisms responsible for common infections in pediatrics. Thus, this group should be relegated to the position of limited purpose drugs, prescribed only if other more effective and less toxic antimicrobials cannot be administered, as well as in a few, relatively specialized situations. Even in hospitalized patients, the tetracyclines find limited usefulness.

I would like to emphasize I am dealing here again, with children.

Senator NELSON. When you say even in hospitalized patients, you are referring to——

Dr. EICHENWALD. Children.

Senator NELSON. Pediatrics.