There are two further footnotes that I would like to make for the record with respect to digoxin tablets: First, the worst problem in bioavailability of digoxin tablets emerged in Great Britain with the original producer of this drug, the manufacturer who had had the lengthiest experience, the largest production in the United Kingdom. Serious problems were encountered with bioavailability that they did not know about, but which were discovered only later in practice, and they were serious because of the widespread use of that manufacturer's product.

Furthermore, the problems of bioavailability in Scandinavia were minimal, and in my opinion one of the reasons for that is that the Scandinavian Pharmacopeia sets standards not only for the finished tablets, but also gives a specified formulation, that is a fixed formula, for digoxin tablets. It says it must possess digoxin and only certain other inert ingredients which it enumerates, and then says it shall be punched in a certain manner.

One of the difficulties in this country was that manufacturers used their own imagination in incorporating inert ingredients and punching in any manner that they wished, and consequently some of these other ingredients interfered with the dissolution of digoxin from the tablet. That was one of the factors.

So in my opinion, this fixed formula, this requirement of the Scandinavian Pharmacopeia did eliminate some of the bioavailability problems.

Mr. GORDON. Why do we not have a fixed formula for all drugs?

Dr. BANES. That has been suggested, but that has never been a principle in the standardization of drugs for the most part in this country. I should say that there are fixed formulas for some types of products, and such formulas are in both the U.S. Pharmacopeia and the "National Formulary". Such articles as phenobarbital elixir have definite fixed formulas. Anything which purports to be phenobarbital elixir USP must be made in accordance with that formula. But that is true only of a small number of drugs in the United States.

Mr. GORDON. If you have a fixed formula, then, for most drugs, you would not have a problem of bioequivalency, is that correct?

Dr. BANES. Well, I think that would be too sweeping a statement. I would hesitate to predict. It is always risky to prophesy, and I am sure problems will emerge. But in my opinion, with certain drugs such as digoxin tablets, a fixed formula which is known to deliver the active ingredient in a predictable manner would be helpful. It might be helpful for some of the most important drugs, among which I would include digoxin tablets and digitoxin tablets.

Senator NELSON. Thank you very much.

Mr. Adams?

Mr. ADAMS. Just one question, Dr Banes.

As to the drugs that have a bioavailability problem, regardless of the number, are there any general statements you can make about them?

That is, are they all new drugs or new combinations?