In the judgment of our Bureau of Medicine, the novobiocin component of Panalba is most likely responsible for the blood dyscrasias.* Yet the use of novobiocin for tonsillitis could only be justified if the infecting organism was staphylococcus; and had that been determined, the anti-staphylococcus drug of course would hardly have been novobiocin in a fixed combination providing half the usual dosage, especially since the advent of the semi-synthetic penicillins.

Another aplastic anemia report concerned a 6-year-old girl, given Panalba for tonsillitis and ear infection. She also developed both a rash and aplastic anemia. She recovered eventually. Throat cultures were not made in either of the two above cases, so there is no way to determine whether the novobiocin component of Panalba played any therapeutic role in the infection.

In reviewing the Upjohn files, we found that in one instance a physician in the western part of the country reported to Upjohn in 1963 that he was experiencing "almost routine reactions in patients receiving Panalba."

Unfortunately, as the American Medical Association is well aware, adverse drug reactions are grossly under-reported, so we have no way of estimating the true incidence rate of adverse reactions to Panalba. But I think it is reasonable to assume that the novobiocin component increases the risks of adverse reaction; and of course with regard to potential liver toxicity, the two drugs in the combination of tetracycline and novobiocin overlap.

In evaluating the risk/benefit ratio of the fixed-combination novobiocin drugs, this Administration also took into account blood level studies in which the novobiocin and tetracycline levels were assayed. It became increasingly apparent, in the course of reviewing both Upjohn and FDA blood level records, that the novobiocin levels obtained with Panalba administration were not as high as those obtained when novobiocin was administered alone. In other words, novobiocin in Panalba does nothing to improve the action of tetracycline against organisms susceptible to it. Moreover, when the organism is a staphylococcus which is resistant to tetracycline, novobiocin is in effect being used alone, in inadequate dosage or with excessive dosage of tetracycline, and in a product which provides lower blood levels than if the single drug were being administered *without* the tetracycline.

Finally, this Administration was not unmindful of the opinion of experts in anti-infective medicine, across the country, who have expressed themselves in journal articles and editorials for the past few years, in opposition to the use of fixed combinations drugs such as Panalba.

Dr. William McCabe of Boston has stated that "combinations of tetracycline with agents such as novobiocin and oleandomycin afford no therapeutic advantage." (Antimicrobial Agents and Chemotherapy 1967, p. 226).

The New England Journal of Medicine has editorialized: "It is discouraging and disquieting that, in spite of repeated expositions of the defects of the fixed combinations and the potential or actual dangers of their application, they are still being prescribed in sufficient quantity, both here and abroad, to encourage the manufacturers in continuing their production and in promoting their use. It cannot be too strongly emphasized that the best interest of the individual patient is served and the least harm done when antibiotics are prescribed, each in its optimum dosage and only for infections in which it is specifically indicated. Their possible curative and life-saving properties will also best be preserved for other patients if they are always used only in this manner." *262*:255–6(1960).

Dr. Harry F. Dowling, former Chairman of the A.M.A. Council on Drugs, has said, "In one area there is complete agreement among clinicians working with infectious diseases; there is no need to market fixed combinations of antibiotics." (Antimicrobial Agents and Chemotherapy 1967, pp. 134–5).

We hope this information is helpful to you and the A.M.A.

Sincerely,

HERBERT L. LEY, Jr., M.D.,
Commissioner of Food and Drugs.

Mr. HARRISON. In the August 4 issue of the American Medical News here, is a two-column article, "FDA Officer Explains Combination Decision."

We will be glad to provide that article for the committee.[1]

Senator NELSON. Thank you.

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*Blood dyscrasias are a well recognized toxic effect of the administration of novobiocin (1965 edition of New Drugs, Evaluated by the AMA Council on Drugs, 1965, p. 45).

[1] See pp. 5604–5605.