

5. Other Adverse Reactions that have been reported include: bulging fontanelles in infants under one year of age, anaphylactoid purpura, granulocytopenia and exfoliative dermatitis.

Reference: Diseases of Medical Progress, 2nd Edition, Thomas, 1962 pages 25-26.

B. Reactions to Novobiocin

1. *Hypersensitivity reactions*.—Cutaneous eruptions of varying severity have been reported as occurring in from 7-20% of individuals in series reported in the United States. One foreign report cites 53% of cases treated with novobiocin developed a typical maculopapular exanthema. In many cases drug fever accompanied the rash.

Other reactions including angio-edema, serum sickness. Stevens-Johnson syndrome, are rare reactions that have been reported.

References: Diseases of Medical Progress, 2nd Edition, Thomas, 1964, pages 31-32. Side Effects of Drugs, Fourth Edition, Excerpta Medica Foundation, 1964, pages 193-194.

2. *Blood Dyscrasias*.—Eosinophilia and leucopenia (approximately 1%) are fairly frequent reactions, usually associated with skin reactions. Thrombocytopenia, agranulocytosis and pancytopenia have been reported rarely.

3. *Hepatotoxicity*.—Novobiocin-induced jaundice due to hyperbilirubinemia in infants was reported soon after the drug was first marketed.

One report indicates that hepatomegaly with jaundice occurred in 22% of cases treated.

References: Diseases of Medical Progress, 2nd Edition, Thomas, 1964, pages 31-32. Side Effects of Drugs, Fourth Edition, Excerpta Medica Foundation, 1964, pages 193-194.

C. Adverse Reactions to "Panalba"

Submitted by The Upjohn Company to FDA and include the following:

Blood Dyscrasias, 27 (6 fatal). Including thrombocytopenia, leucopenia, eosinophilia, hemolytic anemia, aplastic anemia (pancytopenia).

Hypersensitivity Reactions, 39 (2 fatal). Including minor skin rashes, urticaria, serum sickness exfoliative dermatitis, Stevens-Johnson syndrome and anaphylaxis.

Gastrointestinal Reactions, 44 (none fatal). These include glossitis, stomatitis, nausea, vomiting, diarrhea, anal pruritis. One physician states that approximately 20% of cases treated developed glossitis and another stated that many infants developed thrush (oral moniliasis).

Liver, 7 (1 fatal). These include jaundice and hepatic necrosis.

Central Nervous System, 22 (none reported as fatal). These include hyperexcitability in children, headaches (severe), drowsiness, and bulging of the anterior fontanelle in infants.

Dental, 4 cases of tooth staining in children. Based on the estimate submitted by The Upjohn Company that approximately 47,500,000 individuals have received treatment with "Panalba" the following incidence of reactions would be expected based on literature reports of reactions due to either tetracycline and/or novobiocin.

Blood Dyscrasias, 1 percent (leucopenia), 475,000.

Hypersensitivity Reactions, 20 percent (one investigator reported 53 percent), 9,250,000.

Gastrointestinal Reactions, 20 percent (one investigator reports 20 percent of infants develop glossitis), 9,250,000.

Liver, 1 percent, 475,000.

Other miscellaneous adverse reactions—including dental staining in children, headaches, hyperexcitability, bulging of anterior fontanelles—estimated at 2 percent, 950,000.

JOHN J. JENNINGS, M.D.,
Acting Director, Bureau of Medicine.

Senator NELSON. Go ahead, Doctor.

Dr. LEY. It was the judgment of the five anti-infective drug panels that the use of these fixed combinations should be discontinued and that the physician should use individual components according to his best clinical and laboratory information. Citing the increased