

solved at the laboratory level and somewhat by the age level because, when I mention gray sickness, you will see that in infants, where this was a problem because these infants had humidifiers on their incubators, Kanamycin is a less toxic drug than chloramphenicol and replaced chloramphenicol in the newborn nursery.

In the older age group where renal function is naturally deteriorating, chloramphenicol may be a better drug. So in this very restricted area of the gram negative rod pneumonias acquired in the hospital, and which is usually preventable, chloramphenicol may be indicated.

That, as far as I see, is the only respiratory tract use for the chloramphenicol.

In contrast to this potentially favorable effects are some serious side effects. First and foremost, the drug can produce a fatal aplastic anemia, the frequency of which appears to be dose dependent, although not in the sense that Dr. Dameshek used dose effect in the metabolic effect. In other words, there is a susceptible subgroup, but this subgroup can be disclosed to a larger and larger extent by increasing the dose, so it is dose dependent. It is the most frequent aplastic anemia, not associated with a malignancy of a known cause.

This reaction probably is not in exaggeration of the dose related response which is the almost uniform interference by high doses, with blood cell formation due to blocking of protein synthesis, but is more of an idiosyncratic reaction probably of some metabolic origin and is not predictable.

The most recent definitive study in California, which was done at the request of their Legislature, of all deaths from aplastic anemia in the State suggests that aplastic anemia occurs once in about half a million people other than those taking chloramphenicol. Among those taking chloramphenicol the rate for those taking a 5-gram total dose was about 1 in 40,000; a 7½-gram total dose, 1 in 25,000.

While these rates were low, it should be noted that the doses were also quite low. As a matter of fact, the package insert recommends 50 to 100 milligrams per kilogram per day. Most adults weigh 50 to 70 kilograms, so the recommended dose is from 3 to 6 grams. This obviously means that most of the patients in the California study were treated with ineffectual drug levels.

There is no good evidence in the literature that bacterial diseases will respond to doses lower than those recommended, although the rickettsial diseases will respond to as low as 25 milligrams per kilogram in short courses. So they will respond to a total dose of something like 10 grams, 2 grams a day for 5 days, in a medium-sized adult.

However, typhoid fever was shown not to respond to less than 50 milligrams per kilo per day, or a 3-to-4-gram-a-day dose. These are the only diseases in which they are a really good study on a dose effect curve for a disease.

Mr. GORDON. I note in the publication from California, the report to the California State Assembly, dated January 1, 1967, in table 16 in the back, it says that the estimated mean grams of chloramphenicol received per patient is 9.55, 1965 to 1966. What is the significance of that particular dosage?

Dr. LEPPER. This indicates that the vast majority of patients receiving chloramphenicol get an inadequate dose for the purposes for