Senator NELSON. The figure used on the incidents of aplastic anemia from the California study—I'm not exactly clear from my memory how that study achieved the statistics. It was the opinion, I believe, of Dr. Wehrle, who testified yesterday, that these statistics were gathered from death certificates. Is that correct?

Dr. LEY. If I may, Senator, I would like to outline the details of the California study leading to the determination of two separate risk incidents of aplastic anemia following chloramphenicol administration, and I'm referring specifically to the summary at the beginning of the California report.

The California group chose from death certificates filed in California for an 18-month period all those who were related to hematologic disorder. They then separated from these patients who had aplastic anemia and subsequently those that had fatal aplastic anemia. From this culling——

Senator NELSON. These were all death certificates?

Dr. LEY. These were all death certificates. That was the basic source of information. From this culling they uncovered 10 patients who had received chloramphenicol who died from aplastic anemia. This gives a numerator figure. For the denominator the total number of patients in California who had received chloramphenicol over the same period, they then made a survey of physicians and pharmacies to determine the usage. And they estimated that 220,000 patients had received chloramphenicol over the corresponding period.

There is one other computation which is critical here in arriving at the risk figure which the California group published in the determination of the average dosage per patient of chloramphenicol, I read directly from the report.

"If the risk is calculated on the average dose of 4.5 grams during 1965, the risk is one in 40,500."

Senator NELSON. Would you please start that sentence over again.

Dr. LEY. "If the risk is calculated on the basis of an average dose of 4.5 grams per patient"—that was my insert—"during 1965, the risk"—and I insert "of aplastic anemia developing"—"is one in 40,500." The next sentence, "If the risk is calculated on the basis of an average dose of 7.5 grams—I insert "per patient"—"it"—the risk—"is one in 24,200."

These were the two figures of risk identified by the California group which bracketed in their opinion the probability of the chloramphenicol-receiving patient developing aplastic anemia.

Senator NELSON. Well, doesn't this extrapolation made from these statistics have a built-in conservative factor; that is, you find 10 cases reported to have died from aplastic anemia. How often are you going to have cases in which the drug was prescribed for a nonindicated case and the physician simply isn't going to report that this was the case?

Dr. LEY. There is a possible bias here in the initial failure to report a death due to aplastic anemia. It could introduce a bias as you suggest. Death certificates are now required in all of our States and must indicate a specific diagnosis, primary diagnosis as the cause of death. The group chose those death certificates in which physicians had entered the diagnosis, aplastic anemia, as the cause of death. Now, it is possible that they may have been some death certificates that did not include this information. That is a possibility in the study.