8. Granules of p-AMINOSALICYLIC acid were shown to be less than 50 percent available when compared with the pure drug and compressed tablets of the sodium and calcium salt (Middleton, et al: *J. Can Pharm. Sci., 3:* 97–101, 1968);

9. The absorption of ASPIRIN was shown to be significantly different in tests between the seven leading brands (Levy G.: *J. Pharm. Sci., 50:* 388–392, 1961);

10. RIBOFLAVIN'S bioavailability was found to be directly related to tablet disintegration time, and there were large differences between several formulations (Morrison, et al: *J. Amer. Pharm. Assoc. Sci. Ed., 48:* 634–647, 1959).

There have been several other studies involving drugs such as ephedrine, warfarin, dicoumarol and others, showing similar results of wide variations in availability of the drug at the physiological level. In a total of twenty-four scientifically controlled studies in man, eighteen (75 percent) show definite discrepancies with therapeutic implications and an additional four have equivocal results. Thus, 91 percent of controlled studies in which the microbiological, chemical and physical tests meet established standards demonstrate physiologic inequivalency.

B. CLINICAL REPORTS

The clinical evidence of physiological inequivalency is likewise compelling. There have been reports of clinical observations where two or more products containing the same drug in the same dosage form did not result in equal therapeutic results. For example:

1. Campagna relates an incident where his patient was maintained on a standard dose of PREDNISONE. When the patient was admitted to the hospital for another matter he received a different brand of prednisone resulting in an exacerbation of the original condition and hence an extended hospital stay. When the patient was returned to the original brand of prednisone, the condition was again brought under control; (Campagna, et al: *J. Pharm. Sci. 52:* 605–606, 1963);

2. In another example, reported in the *Canadian Medical Association Journal,* a patient requested his physician permit the pharmacist to dispense a cheaper brand of TOLBUTAMIDE. The patient's diabetes promptly became uncontrollable, the FBS shot up to 287 mg percent, and whole tablets were recovered in the stool; (Carminetsky, S.: *Can. Med. Assoc. J. 88:* 950, 1963; also Carter, A. K. *Can. Med. Assoc. J. 88:* 98, 1963);

3. Catz and coworkers have published reports of THYROID tablets that meet U.S.P. specifications but were ineffective clinically according to PBI determinations. (Catz, et al: *New Engl. J. Med. 266:* 136–37, 1962, et seq.);

4. Several epileptic patients who had been stabilized on DILANTIN dosage suddenly showed signs of toxic overdosage. The cause was directly traceable to a change in the inert filler in the capsule from calcium sulfate to loctose which resulted in an increase in absorption of the active ingredient (Rail, L.: *Med. J. Australia 2:* 339 (Aug. 10) 1968, et seq);

These reports, both scientific and clinical, are no cause to indict all drug products. But it does seem abundantly clear that clinical equivalency, or bioavailability or whatever identification it has, is of significant practical importance to the physician and to the pharmacist and, ultimately of course, to the patient.

Some people claim that this small number of examples out of the thousands of drugs available are, in themselves, a measure of the relative insignificance of the problem. The implication is that we should accept that a certain small percentage of our drugs will be ineffective and prescribe all drugs by their official name. Others, however, point out that we really don't know the magnitude of the problem because too few studies have been done. To assume that there is no problem without studying its magnitude, is not rational. It is within this dichotomy of opinion that physicians continue to prescribe by trade names in order to assure themselves that their patients will obtain effective drug products. We cannot ask them to change their practice unless we are prepared to assure them by other means that the quality of the medication their patient receives is satisfactory.

This matter cannot be dismissed lightly by saying that all USP drugs are equivalent and that the physician has only to prescribe by the USP name and thus great savings will be made. There are too many prestigious organizations deeply concerned about the question of bioavailability. The interest of the Division of Medical Sciences of the NAS/NRC in the problem of bioavailability testing tends to support the current practice of physicians to prescribe by trade