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THE INTERFACE OF ANIMAL AND CLINICAL PHARMACOLOGY

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SUMMARY

In considering the factors of safety and efficacy in the development and evaluation of new drugs, a continuous interplay between clinical and animal pharmacology must take place. Useful determination of efficacy in compounds such as steroidal contraceptives requires very large numbers of subjects, and cannot be performed adequately in animal experiments. On the other hand, essential knowledge of pharmacokinetics requires animal experimentation in a species which shows close resemblance to man in the metabolism of the agent under study. High-dose, short-term toxicity studies in animals may not successfully indicate areas of concern in clinical studies, especially if the side-effect has a low incidence. Studies of mechanism of action may be helpful after a worthwhile degree of safety and efficacy has been demonstrated, or in developmental studies where analogues are being screened.

The subject of this discussion is the clinical pharmacology of a theoretical new compound having weak proestrogenic, potent antiprogestational, and no androgenic activity, effective orally, to be used on days 24–28 of each cycle.

The classical pharmacological questions which are usually asked, and which have been suggested for such a discussion, are as follows:

1. Selection of dose levels.
2. Parameters to be studied:
   i. Pharmacodynamics
   ii. Human metabolism of compound—how important?
   iii. Endocrine parameters–what, how often, how long?
3. Special problems:
   i. Administration in very early pregnancy
   ii. Reversibility
4. Other metabolic parameters.
5. Necessity for study of:
   i. Endometrial morphology
   ii. Endometrial enzymes including histochemistry
   iii. Endometrial progesterone receptors
   iv. Functional morphology of corpus luteum

It is the purpose of the following comments to contrast this approach, representing classical pharmacology, with another approach which might be termed pragmatic clinical pharmacology.

The primary data to be obtained from a clinical trial, the items which must be investigated in Phase I through Phase III, are, in order of importance, *effectiveness*, *safety* and *acceptability*.

The last of these can be disposed of first. The last two decades of clinical experience with various contraceptive agents have shown that *acceptability* is an extremely complex phenomenon, with geographic, ethnic, social and even political influences. We have learned that acceptability under the conditions of a rigidly controlled clinical trial may have little relevance to general acceptability under routine medical supervision or in a non-medical demographic dimension. Studies of contraceptive acceptability are in their technological infancy today, and await more closely coordinated protocols which utilize the skills of sociologists and medical anthropologists, as well as the usual disciplines of clinical investigation and biostatistics.

The inference that a new drug is clinically *effective* derives from studies in animal species of various kinds. The assumption that the usual experimental animal species are necessarily relevant to human use has been amply disproved. Classical examples are clomiphene citrate, which acts as a contraceptive in rats but as an ovulation stimulator in anovulatory women, and ethynyl estrogens, which are extremely potent pituitary inhibitors in man, while in most experimental paradigms in rodent species they are not outstandingly better than other estrogens.

The horns of the animal-model dilemma are always the danger that an animal model will not reveal biological activity useful in man, and contrarywise, that useful biological activity in the animal model will not be borne out in clinical studies. It is for this reason that we have strongly advocated over the last decade the importance of studying effectiveness and pharmacodynamics in subhuman primates at a very early stage in the development of new compounds. Over the last five years, we have studied a number of abortifacient or other antifertility compounds in subhuman primates, and have demonstrated that promising results in rodent species may not be borne out by appropriate studies in female baboons. The

timely insertion of such subhuman primate studies into developmental animal pharmacology represents a great saving of time and cost by avoiding further small-animal work on a compound which is not likely to prove of value in the human subject. Studies in subhuman primates present unique problems in optimizing the cost-effectiveness of such investigations, but this important aspect is outside the limits of the present discussion.

In the present context, it would nevertheless be valuable to document the stated biological activities of the theoretical compound by appropriate investigations in subhuman primates. The lack of androgenicity would be the most difficult, and might well be deferred for eventual clinical evaluation.

Contraceptive effectiveness must be evaluated in pragmatic terms, since agents which are substantially less effective than those already available are not likely to have much acceptance unless they provide other unique features. The yardstick for effectiveness, in the first instance, would be that of the oral contraceptives which in general use, reduce the pregnancy rate to about 1 per thousand women per year.

Events of this degree of infrequency create difficult statistical problems and demand large-scale clinical trials. The following figure is a device for estimating required sample size based on a zero pregnancy rate during a clinical trial. It will be seen that a sample size of about 5000 cycles with *no* pregnancies is required to give a statistical upper 95% confidence limit which assures contraceptive effectiveness of an order competitive with the standard oral contraceptives. A table for estimating the confidence region in such studies, when zero to 2 pregnancies are observed in the series, is shown in Table 1.

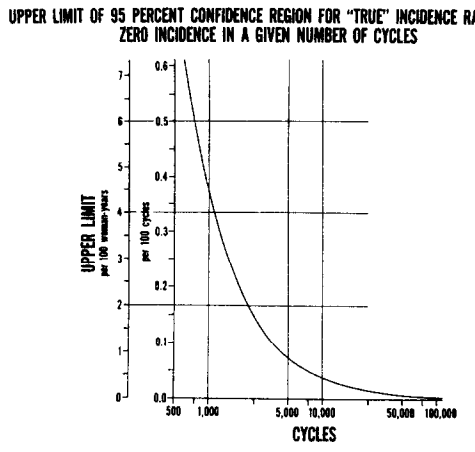

Fig. 1.

It may well be that the development of our theoretical compound has not reached the stage where clinical trials of this magnitude can be undertaken. To test the effectiveness of the compound in a gross way, in a small number of subjects, requires a knowledge of the mechanism of action, together with some clinically acceptable way of detecting it. If, for example, the theoretical compound were luteolytic, appropriate studies such as plasma progestins could be used to demonstrate the existence of this mechanism in human subjects. It will be observed that the question answered by such experiments is entirely different from that of the previously described clinical trial, and provides no predictive information as to pragmatic effectiveness.

In actual practice, there is room for debate regarding the priorities to be given to studies of mechanism

Table 1

No. of pregnancies	No. of cycles	95 Per cent confidence region (per 100 woman-years)	
		Upper limit	Lower limit
0	100	44	0.00
1	100	67	0.30
2	100	86	2.9
0	500	8.9	0.00
1	500	13.4	0.06
2	500	17.3	0.58
0	1,000	4.4	0.00
1	1,000	6.7	0.03
2	1,000	8.6	0.29
0	5,000	0.89	0.00
1	5,000	1.34	---*
2	5,000	1.73	0.06
0	10,000	0.44	0.00
1	10,000	0.67	----
2	10,000	0.86	0.03
0	25,000	0.18	0.00
1	25,000	0.27	----
2	25,000	0.35	----
0	100,000	0.04	0.00
1	100,000	0.07	----
2	100,000	0.09	----

* Extremely small but not zero.

of action vs clinical trial evaluation of efficacy. Both involve a considerable degree of effort, though of a different kind, and substantial expense. Studies of the mechanism of action are useless if a compound does not have sufficient effectiveness. On the other hand, maximum effectiveness can only be surmised, unless the exact mode of administration, the duration of action, etc. are optimized by appropriate pharmacodynamic studies.

In this connection, the importance of well-designed pharmacodynamic studies cannot be over-emphasized. Knowledge of the behavior of the compound in the human being and in a comparable animal model may be crucial. Examples of this situation are well known. ORF-3858 is a weakly estrogenic compound, which was blastocidal in the usual laboratory animals and in monkeys as well. In human Phase I clinical trials, it turned out to be disastrously ineffective. Later studies revealed that the compound was excreted very rapidly in the human subject, making it unlikely that effective target site levels could be maintained. The discouraging clinical experience played a considerable role in abandoning research on this and related compounds at the time. The reverse situation is illustrated by the unfortunate selection of the canine species to study 17-acetoxy progestagens. Aside from the peculiarities of the dog, which make it unsuitable for studies of this kind in general, it was subsequently demonstrated that the metabolism of this class of compounds was much slower than in human subjects, so that the calculated mg-per-kilo doses administered were, in fact, 90–200 time greater than estimated on the standard basis. This massive overdosage, combined with selection of the improper test species, has raised issues concerning the safety of 17-acetoxy progestins which, in our opinion, are entirely irrelevant to human use but, nevertheless, have created major obstacles to approval and widespread use of these substances. This problem, together with the enormous expenditure of time and money, could have been avoided by more appropriate and thoughtful animal pharmacology.

The question of *safety* includes not only the standard toxicological questions, but the overriding question of the effects of the hypothetical compound on an early implantation, since presumably the drug is to be given on cycle days 24–28, by which time implantation may have occurred. Fortunately, both in the subhuman primate model and in the human volunteer, it is now possible to identify chorionic gonadotropin β-subunit before the first missed menstrual period. It is obvious that such assays need to be done in female baboons exposed to timed matings, as well as in human subjects who volunteer for endometrial aspiration at the end of the cycle or for later interruption of the pregnancy, should it persist in spite of the treatment. Such experiments clearly are the initial stage of these investigations, and provide basic physiological information as well as initial pharmacological insights. Dose and treatment-duration factors, histological effects on endometrium and related parameters can be examined by recognized methods, provided the ethical questions of human experimentation can be satisfactorily resolved.

Needless to say, such experiments do not provide any estimate of the degree of safety, which must be investigated by expanded trials of a clinical nature. In the final analysis, one will once again come across the exceedingly difficult questions posed by the possible occurrence of rare events, as is implicit in the question of fetal malformations and related problems.

The purpose of this brief and very sketchy discussion has been, primarily, to demonstrate an alternative to classical pharmacological thinking, which involves lengthy experimentation in animal models of unproved relevance, investigations of mechanism of action, etc. By contrast, we feel that the early and intensive use of subhuman primates, followed by clinical investigations designed to elucidate factors of efficacy and safety require primary attention. Interdigitated with these efforts, there should be investigations of pharmacodynamics and mechanism of action, along lines which are directly relevant to the questions of effectiveness and safety. It seems superfluous to say that studies of basic pharmacology are pointless for a compound that will never be used clinically (unless it serves as a pharmacological model for other compounds) and that compounds which do show sufficient clinical promise will eventually require appropriate basic studies to define their pharmacological properties in greater detail.