# Controversies in Contraception

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# Preface

The era of modern contraceptive technology began about two decades ago when steroidal contraceptives and intrauterine devices were introduced for clinical use. The initial enthusiasm generated by these potent fertility regulating agents and devices was soon followed by reports of troublesome side effects and occasional severe complications. Clinicians, basic scientists and epidemiologists began to investigate painstakingly the relationship of steroidal contraceptives to thromboembolic diseases, metabolic and nutritional changes, breast and uterine neoplasia, endocrine disorders and persistent infertility. Others studied possible hazards of IUDs. Protagonists and antagonists hotly debated their points of view both in scientific and lay publications. Inevitably, in the emotionally charged atmosphere many unsubstantiated claims and allegations were made. Added to these were conclusions drawn from anecdotal reports, ill conceived and pseudoscientific investigations, extrapolation from animal experiments and some well planned and not so well planned retrospective studies.

Steroidal formulations and IUDs are used by millions of healthy women in the world who are subject to the same health problems as the nonusers. Objective evaluation of health hazards caused by fertility regulating agents and those brought about by natural causes or environmental and toxic substances may be a difficult or even an impossible task. A prime example of this situation is found in the association of steroidal contraceptives and smoking in the etiology of myocardial infarction. A careful analysis of the available data indicates that the risk of nonfatal myocardial infarction in oral contraceptive users is not greater than that among nonusers, but the combination of smoking and oral contraceptives significantly increases the risk.

It is fair to state that there are very few adequately planned prospective studies relative to the major side effects of contraceptive agents.

Another source of difficulty is related to occasional hasty decisions made by drug regulatory agencies based on less than satisfactory scientific data. Needless to say that both the medical profession and the public are confused and regard with skepticism all new information until it is adequately confirmed. What is needed is a careful scrutiny of the benefits and risks of fertility regulating methods in current use. It is not sufficient to present real or imaginary mortality or morbidity figures of various contraceptive methods without comparing them to the risks of unwanted pregnancies.

*Controversies in Contraception* was born out of necessity to clarify some of the controversial and confusing issues in the field of fertility regulation.

Controversies are not new in medicine nor should they be considered unhealthy. For, out of divergences of opinion, the truth is likely to emerge.

The chapters of this book are based on materials presented at the Harold C. Mack Symposium held in Detroit in September, 1977. The contributors, who are among the leading clinicians and scientists in the field of contraceptive technology, were assigned the task of reviewing the available information and presenting an unbiased view of the most controversial topics.

The editor is most grateful to the authors for the excellence of their articles and for their efforts to contribute to this volume.

Thanks are also due to Marlene Visconti for editorial assistance and to Williams & Wilkins for their collaboration and superb production of this book.

The editor is hopeful that the chapters of this monograph will serve as a practical guide and source of reference for all physicians, nurses and other health-related personnel who are faced daily with the task of counseling their patients, the women who desire to safely control their reproductive function.

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CHAPTER 1

# Relative Potencies of Oral Contraceptives*

Richard A. Edgren, Ph.D.

Potency is a relatively unimportant characteristic of a drug since it makes little difference, whether the effective dose of a drug is 1 μg or 100 mg, as long as the drug can be administered in appropriate dosage. Potency is not necessarily correlated with any other characteristic of a drug, and there is no justification for the view that the more potent of two drugs is clinically superior. Low potency is a disadvantage only if the effective dose is so large that it is awkward to administer (Goodman and Gilman, 1975).

## INTRODUCTION

Despite its relative lack of importance the potency of drugs receives an unconscionable amount of attention and the basic concept is applied and misapplied repeatedly. Not infrequently it is distorted to fit preconceived

* I am indebted to Drs. G. S. Berger and P. P. Talwar of the International Fertility Research Program for permission to quote from their unpublished paper and to the Endocrine Society for permission to reproduce Figure 1.6. The quotations from Goodman and Gilman are courtesy of the MacMillan Co.

notions. Recently, Edgren & Sturtevant (1976) reviewed aspects of the problem of potency as it applied to oral contraceptives. This chapter will expand on certain of these considerations.

## THE BASIC DEFINITIONS

### What is Potency?

Fingl and Woodbury (1970) define potency of a drug as: "The location of its dose-effect curve along the dose axis. . . ." For those who are not accustomed to thinking in such terms, every drug produces a series of effects in a responsive organism. One of these responses is normally isolated as the desired therapeutic effect; all others are side effects. All such actions may be graded in intensity, although this gradation will vary with the nature of the response. For example, estrogenic hormones produce increases in weights of the uteri of laboratory animals. This response forms a smooth continuum on a curve. In contrast, in any given month, and under any specific estrogen treatment schedule, a woman may or may not ovulate. Since she cannot have a "partial" ovulation, we have a discontinuous phenomenon and ovulation or its blockade must be treated as a proportional response.

Irrespective of which type of data are generated most drugs tend to produce greater intensities of response at higher doses and lesser intensities at lower doses. Dose-effect curves are usually more or less sigmoid in shape, and as stated by Fingl and Woodbury potency is the position of the curve on the abscissa, the dose-axis (Figure 1.1). In these conditions, absolute potency is indicated as the dose that produces a given effect, in whatever units may be meaningful, i.e., 2 mg/kg, 10 mg/woman, 0.1 μg/mouse, etc.

When a second drug is considered the problem of potency, now relative potency, becomes manifestly more complex. Figure 1.2 introduces the problem. Here we have two dose-effect curves that are identical except for position along the dose axis and relative potency is simply measured as the distance between the curves along the abscissa. The line 1 distance may also be expressed as some function of A/C and is identical to the length of line 2 or B/D. Figure 1.3 adds the complication of nonparallel dose-effect curves. Here drug I has a steep slope and that for drug II is shallow. The potency of drug II relative to drug I could be measured by the length of line 1 or A/B or by the length of line 2 B/C. However, B/C > A/B so no single relative potency can be assigned. In this situation the concept of relative potency is

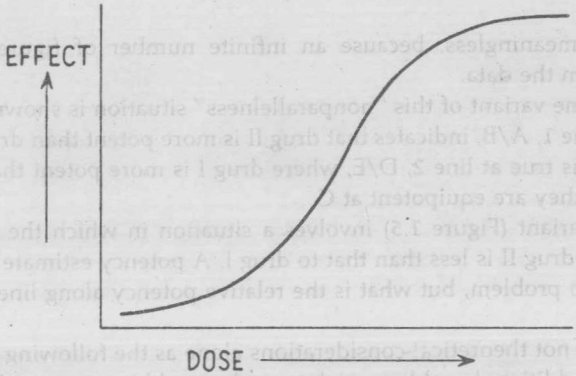


**Fig. 1.1.** Generalized dose-effect curve for a drug.

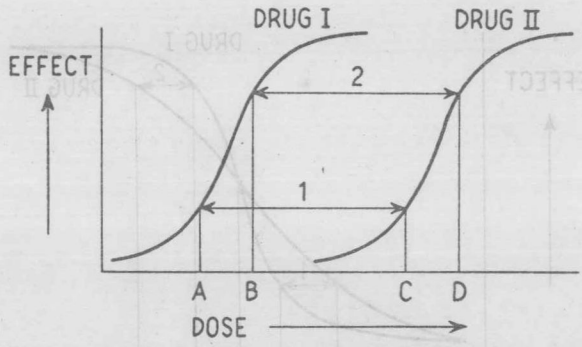


**Fig. 1.2.** Generalized dose-effect curves for two drugs that differ only in potency.

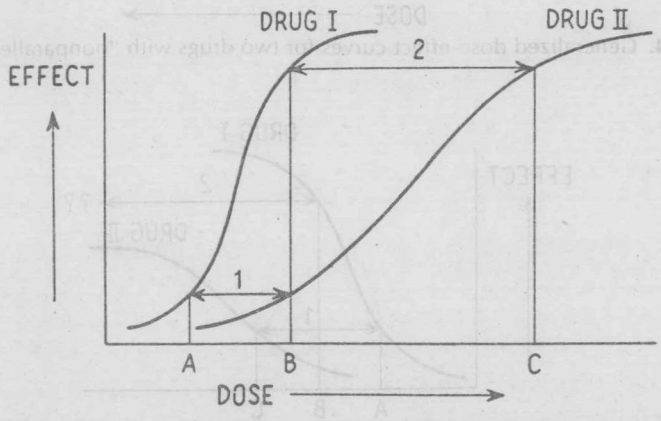


**Fig. 1.3.** Generalized dose-effect curves for two drugs with "nonparallel" curves.

essentially meaningless, because an infinite number of figures may be evolved from the data.

An extreme variant of this "nonparallelness" situation is shown in Figure 1.4. Here line 1, A/B, indicates that drug II is more potent than drug I, while the reverse is true at line 2, D/E, where drug I is more potent than drug II; and finally they are equipotent at C.

A final variant (Figure 1.5) involves a situation in which the maximum response to drug II is less than that to drug I. A potency estimate along line 1, A/C is no problem, but what is the relative potency along line 2? B over what?

These are not theoretical considerations alone as the following discussion will show. Additional problems and examples could be given such as curves that go up and then down and *vice versa*. Thus, *Dose-effect curves come in*

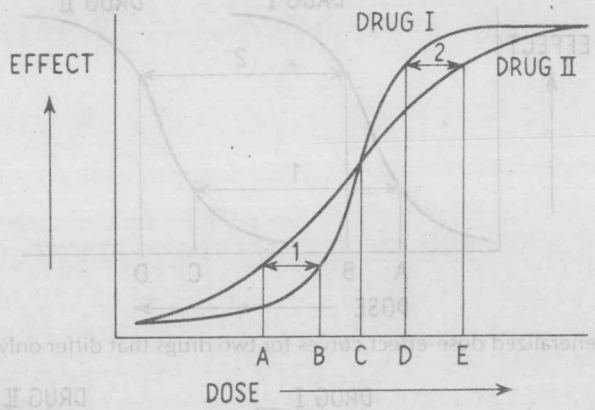


**Fig. 1.4.** Generalized dose-effect curves for two drugs with "nonparallel" curves.

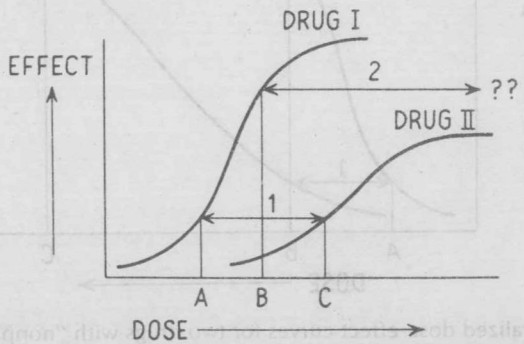


**Fig. 1.5.** Generalized dose-effect curves with differing maximal values.

*widely varying forms and shapes that affect comparative potency evaluations to the point where simple figures are likely to have little real meaning.*

## How Potencies are Derived

In practice, in the laboratory or in the clinic, one can seldom gather sufficient data to permit full evaluation of a dose-effect curve, and the mathematical complexity of handling such curves has led to various manipulations that permit conversion of the data to simple, usually linear, curves. However, first the data must be gathered; although this is often a simple procedure in the laboratory, in the clinic it may be exceedingly difficult, leading to the dearth of good quantitative data on many aspects of the actions of oral contraceptives and their components in humans.

### *Laboratory Animals*

Some years ago the uterine growth effects of norethynodrel and norethindrone were compared in mice by oral and subcutaneous routes of administration (Edgren, 1958). Mouse uterine growth assays were routine in my laboratories at the time: 21-day old mice were shipped from the breeder on Monday, arrived on Tuesday, were injected on Tuesday, Wednesday and Thursday and sacrificed for autopsy on Friday. Uterine weights were collected from groups of 8–10 mice at varying doses of both compounds over several weeks. The data were pooled, doses transformed to Napierian logarithms and fit to linear curves by the method of least-squares (Figure 1.6). It should be obvious from what has already been discussed that

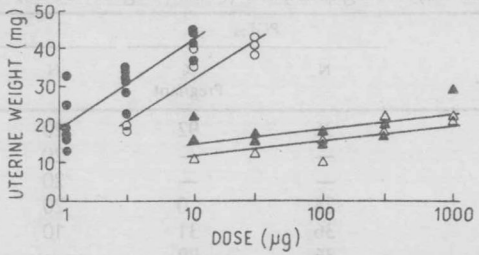


**Fig. 1.6.** The uterine growth-stimulating effects of norethynodrel (dots) and norethindrone. Solid symbols, subcutaneous administration; hollow symbols, intragastric route. Each point represents the mean of 8–10 mice. Regression lines calculated by method of least squares. Simultaneous oil control groups average about 12 mg. in uterine weight (After Edgren, 1958).

assigning relative potencies for these compounds would be gratuitous because a) the slopes of the curves differ grossly; b) the greatest effect of norethindrone is hardly different from controls; and c) both the lowest and the highest doses of norethindrone produce responses similar to those of the lowest dose of norethynodrel. This latter point could be used to justify potency estimates for norethindrone as high as 10% or as low as 0.1% norethynodrel. However, the data clearly indicate that oral norethynodrel is about one-third as potent as parenteral norethynodrel. The data suggest that norethindrone is about one-tenth as potent orally as parenterally, but the shallow dose-response curve slopes and the variability of individual points hardly inspire confidence in any estimate.

Another approach, involving quantal rather than quantitative data, is our current assay for the "luteolytic" effects of prostaglandins. We know that hamster pregnancy is dependent upon ovarian progesterone and that PG's cause histological regression of the corpus luteum, a fall in circulating progesterone and fetal resorption (hamsters, like rats, resorb fetuses; they do not abort). In the assay as it functions, an arbitrary high dose of PG is selected and injected on the afternoon of day 5 of gestation; the animals are sacrificed on day 12 (prior to the expected time of delivery) and graded as pregnant or nonpregnant. Table 1.1 shows exemplary data on $PGF_{2\alpha}$ and $PGE_2$. If the initial dose is effective the compound is retested at about ⅓ the initial dose; this is repeated with progressively decreasing doses until the effect is lost; the data are expressed as an approximate $ED_{50}$. Such niceties as parallelness of slopes are ignored until significant interest has developed in a specific compound. In the case of $PGF_{2\alpha}$ and $PGE_2$, the slopes are parallel (Figure 1.7), or more technically correct, their slopes are not significantly different.

For a final example from animal studies let us examine some data from

**Table 1.1.** Termination of pregnancy in hamsters with a single dose of prostaglandin on day 5 of gestation. (From Edgren *et al.*, 1977)

| Dose (μg) | $PGF_{2\alpha}$ | | $PGE_2$ | |
|---|---|---|---|---|
| | N | % Pregnant | N | % Pregnant |
| Control | 36 | 92 | 20 | 90 |
| 1000 | — | — | 20 | 0 |
| 300 | — | — | 20 | 25 |
| 100 | 24 | 0 | 20 | 90 |
| 30 | 36 | 31 | 10 | 100 |
| 10 | 36 | 89 | — | — |
| 3 | 36 | 86 | — | — |
| 1 | 12 | 92 | — | — |
| Approx. $ED_{50}$ | 21.4 μg | | 229 μg | |

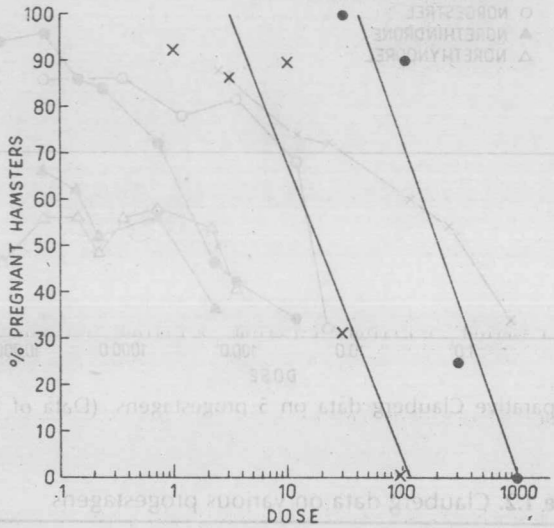


**Fig. 1.7.** Pregnancy terminating (luteolytic) effects of prostaglandins in hamsters.

$X$ $PGF_{2\alpha}$

$y = 128.38 - 62.00 \log \text{dose}$

slope $= 62.00 \pm 19.30$

$PGE_2$

$y = 214.22 - 71.64 \log \text{dose}$

slope $= 71.64 \pm 17.22$

the Clauberg test. Immature female rabbits are primed with estrogen for 6 days and then receive test compound daily for 5 days; at autopsy, 24 hours after the final injection, the uteri are removed and sectioned for histological grading on the standard scale of McPhail. This scale is highly subjective and segments the proliferation of uterine glands from 0–4. The data on selected progestagens are shown in Figure 1.8. To get a single-figure estimate of potency for reference purposes we have arbitrarily chosen to compare compounds at the dose required to produce a +2 McPhail index. Table 1.2 shows the data extracted from the curves, and the numbers of animals that were required to produce even these rather tenuous data. They can, by the way, be improved considerably by employing a log-log transformation i.e., conversion of response to logs as well as dose. This expedient straightens the curves nicely, at least for norgestrel (Edgren *et al.*, 1967c).

These discussions could be extended with an almost infinite number of examples. *Suffice it to say here that practical considerations are such that*

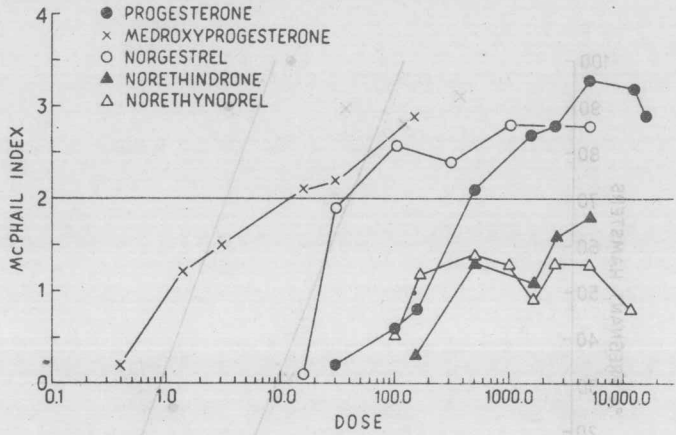


**Fig. 1.8.** Comparative Clauberg data on 5 progestagens, (Data of Jones *et al.*, 1966).

**Table 1.2.** Clauberg data on various progestagens

| Compound | N | + 2 Dose (μg) | Potency (%) |
|---|---|---|---|
| Progesterone | 657 | 450 | 100 |
| Medroxyprogesterone acetate | 50 | 12 | 3800 |
| Norgestrel | 84 | 35 | 1300 |
| Norethindrone | 704 | >5000 | C10 |
| Norethynodrel | 66 | ? | ? |

*we must usually work with less than optimum data, even in the laboratory, and often must make do with crude estimates that ignore such critical factors as slopes, maximal limits, etc.* When important, various experimental designs can be introduced to minimize the impact of such difficulties, but they are beyond the scope of this essay.

*However, in employing such potency data the pharmacologist is, or should be, well aware of their limitations.* These were given due consideration during the development of the oral contraceptives (OC's). As is well known these drugs are combinations of two components: an estrogen and a progestagen that is most commonly based upon 19-nortestosterone. Since only two estrogens have been employed extensively in oral contraceptives they provided no problem. It early became apparent that ethinyl estradiol was more potent than its 3-methyl ether, mestranol, in most bioassays. The progestagens, by contrast, had a broader base, both chemically and biologically and, therefore, required more extensive comparative work. Assays such as the Clauberg and other approaches to progestational potency were employed to