Editorial

Oral Contraceptives and Hypertensive Disease:
A Cybernetic Overview

SOME pharmacologic advances appear to deepen a long-standing doctor’s dilemma: Is the therapy an improvement over the disease? The question has rather ironic overtones in the matter of oral contraception, which may artificially evoke the hypertensive manifestations often associated with the “disease” it is intended to forestall, but without the redeeming issue. On the brighter side, the plastic condition can help us understand the natural one.

Despite a number of suggestions that hypertension, the most frequent complication of pregnancy, is strongly associated with sodium and water retention and with heightened endogenous estrogen activity, not until recently was the possibility explored that administration of exogenous gonadal hormones might duplicate the association. Suspecting oral contraceptives to be implicated in the hypertension of 11 female patients, each of whom was on the “pill,” the hypothesis was tested by manipulating the medication.1, 2

Three observations satisfied us that a definite correlation existed that was not an artifact of the high incidence of both hypertension and oral contraceptive use in the population at large: (1) In six of the 11 women hypertension made its first appearance after oral contraceptive medication was begun, and in two others previously existing hypertension was exacerbated. (2) In six of the eight women from whom the contraceptive medication was withdrawn, hypertension either markedly improved or was completely corrected; the other two women had long histories of hypertension prior to taking oral contraceptives. (3) Hypertension reappeared when the medication was reinstated in two women, only to disappear again when the drug was withdrawn. Since this report, confirmation of the hypertensinogenic potential of oral contraceptives has come from a number of sources, some of them involving larger samples than ours.3-6 Reversible malignant hypertension has even been associated with pill usage.7 Although hypertension is fortunately a rare side effect, these data do provide another reason for caution in the use of the pill.

A modern researcher must seek at least a portion of his explanation of any hypertensive phenomenon in the renin-angiotensin-aldosterone mechanism, a newly elaborated and still only sketchily understood hormonal concatenation whose function appears to be the regulation of sodium and potassium homeostasis and thus of extracellular and intracellular fluid volumes.

Our laboratory work revealed dramatic and sustained increases in the plasma concentration of the renin substrate in practically all women taking the pill.1, 2 This renin substrate abnormality had been observed in several previous studies, but the possibility that it might have pathophysiologic significance had not been developed, perhaps because the renin substrate had been considered to be normally present in such large excess that any further increase would not increase the rate at which it could react with plasma renin. Our in-vitro studies, however, refuted this thesis. To the serum taken from women on the pill and containing increased renin substrate, we added fixed amounts of purified human renin and compared the capacity to form angiotensin with those of later assays that utilized serum from the same subjects after the substrate had returned to normal on cessation of therapy with the pill. The results suggested a regulatory function or a dynamic rate-limiting influence for changes in the renin substrate concentration because the data indicated that in the presence of the higher substrate levels the
same amount of renin released much more angiotensin. It follows that, if there is a homeostatic adjustment mechanism, the hormonal system should adjust so that less renin would actually be secreted in these circumstances. This adjustment was actually borne out in at least two of our patients on the pill whose serum renin concentration declined in the face of sustained high substrate levels during such therapy. Similar findings have subsequently been reported by two other groups.\textsuperscript{8,9} One implication of these observations is that those subjects who get a pressor response are the ones who cannot adequately suppress their renal renin secretion.\textsuperscript{2}

Obviously, under normal conditions one or a series of buffer feedback mechanisms are busily at work. Thus, the observations that greater amounts of renin substrate can depress the production of renin to a homeostatically appropriate level can account for the return to normal of plasma angiotensin levels and of aldosterone secretion. It is equally obvious that under pathologic conditions these buffer mechanisms are inoperative or distorted in their response. One may speculate that the estrogen-progestogen induced derangements in the renin-angiotensin system are beyond the range of a susceptible person's limited compensatory capacity. When the substrate reservoir is raised after hormone medication in a patient so compromised, normal increments in renin secretion in response to various daily physiologic stimuli could lead to an inappropriately exaggerated angiotensin production and to hypertension.

Such studies have only lifted a corner of the lid on the still mysterious box of estrogen's negotiations with the renin-angiotensin-aldosterone system. They suggest again that while the therapist must seek the nature of the disease he must be even more at home with the nature of health, of those homeostatic mechanisms, the proper operation of which must be restored or surrogated. Surely the most impressive finding in the use of oral contraceptives is not that some women consequently develop hypertension, but rather that the overwhelming proportion of women show only slight or no pressor reaction at all. It may be the normal course that increased estrogen promotes increase in the levels of rate-limiting angiotensinogen, but it is not at all normal for this to result in continued increases of aldosterone release, increased plasma volume, and heightened blood pressure.

The possibilities point to lines for future research. One of the first possibilities to be examined is that of an activator or inhibitor of the renin-substrate interaction. We also need study of the effect of estrogens and progestogens on hepatic biosynthesis of renin-substrate and other proteins. The possibility of a qualitative alteration in substrate molecule remains to be investigated.\textsuperscript{1} Isoenzymes of renin utilizing different substrates are known.\textsuperscript{10} Inasmuch as renal insufficiency and nephrectomy also can produce sharp rises in substrate concentration, estrogen's effect on kidney function warrants closer investigation. Do estrogens react on renal tubules in the same way as mineralocorticoids do? What is the effect of estrogen directly on the adrenal cortex and the secretion of aldosterone? Are these mechanisms operative in the toxemias of pregnancy?

It seems apparent from our studies of pill-induced hypertension that the nub of the problem is patient susceptibility. Unfortunately, we do not know yet, except by trial, who is the susceptible woman. Even the obvious parallel between natural and plastic pregnancy offers no clues, for we have observed hypertensive responses to the pill in women who also manifested no such response in prior natural pregnancy. We need much more coordination and diligence in gathering data on a vast scale so that better guide lines can be established.

A number of factors might explain the susceptible person. Preexisting or occult kidney disease could, by producing retention of inappropriately high levels of renin or by disturbed renal tubular conservation of sodium, mechanically reduce a patient's buffer capacity. Sodium and water-retaining effects of estrogen by a direct renal effect\textsuperscript{11} different from that induced by the renin-angiotensin-aldosterone system, and more pronounced in some individuals than in others, could so insidiously increase
plasma volume as to render other persons more susceptible to the pressor action of a given amount of angiotensin. In this context pill hypertension may be a hydremic hypertension similar in mechanism to that associated with excessive adrenal mineralocorticoid.

In the absence of more meaningful data, it is probably safest for the clinician to administer oral contraceptives with special caution to women with a prior history of hypertension, excessive weight gain and edema during menstruation, a familial tendency to high blood pressure and its consequences, hypertensive abnormalities or renal disease in prior pregnancies, or an edematous sensitivity to salt.

Fortunately, pill-induced edema and hypertension are reversible by stopping the medication. A woman beginning to take oral contraceptives must be monitored frequently. She should be instructed to watch her weight carefully, this being one of the surest and earliest indicators of sodium and water retention. Her blood pressure should be taken no later than 2 months after starting medication, checked frequently thereafter, and compared with an adequately established base line. With these simple precautions the pill may be used as indicated by the clinical situation.

However, abandonment of the medication in the face of hypertensive manifestations represents something of a pharmacologic defeat, especially in view of the essential social role of family planning and the important personal benefits which this type of contraception has provided for the overwhelming proportion of its users. The real challenge is to find the answer in more effective and safer pills. We do not yet know if all the varieties of oral contraceptives now on the market have equal pressor potential and whether or not altering the proportions of estrogen or progestogen might obviate the effects on renin substrate. This would be important information to have. It might also be possible to manufacture a variant prescription especially tailored for the susceptible woman by adding a moiety that would furnish the compensatory function she lacks, or an agent that would suppress renin activity, perhaps an ingredient like spironolactone with its molecular configuration improved for greater aldosterone antagonism. A pharmacologic rebuff that attacks the edema and hypertension at its source—the renin-angiotensin-aldosterone system—might prove equally effective in treating similar reactions in natural pregnancy and might prove superior to the diuresis of various diuretic agents. When we can answer hypertension by maneuvering safely within the cybernetics of blood pressure homeostasis, instead of avoiding it, we can with confidence call the outcome progress.

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References
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