

ness has not yet been worked out. During this period of time, the amount of progestational agent in some preparations has been reduced to about one-tenth its original dosage and the amount of estrogen to about one-third, without loss of contraceptive effectiveness. More dose-response information is clearly needed.

Some of the effects of the steroids appear to be idiosyncratic in that a small number of patients respond uniquely. Unrecognized disease, subclinical disorders, and inborn errors of metabolism are just a few of the conditions which may underlie the idiosyncratic response. We must refine our methods for identifying such patients in order to prevent unnecessary complications.

Many of the metabolic effects, however, are quite commonplace when looked for and the replication of these findings in many different laboratories attests to this. There appears to be a characteristic pattern whereby the metabolic reserve is challenged. When ample reserve exists, the effects become prominent.

Senator NELSON. I do not quite understand that. Would you elaborate on that a bit?

Dr. SALHANICK. In other words, a patient who has some compromise, for example, of liver function will show the effects of the contraceptive agents in terms of excretion or in terms of other metabolic phenomena, including jaundice; whereas the people who have absolutely normal liver function will not show this, and I think this is one reason why older women who have been tested or have been under study with the contraceptive agents have given a larger number of abnormal responses than younger women do, as a rule, are considerably healthier.

I believe that this is an important principle for determining which patients should receive the medications and how often they should be reexamined.

An important aspect of the metabolic changes is that many of them appear to be reversible after short periods of treatment. It may be that many of the alterations would be reversible after long-term therapy, but it is impossible to form such judgments until the appropriate studies are performed.

In the analysis of the use of the contraceptive steroids, the most difficult and important problem is the understanding of the seriousness of the observed changes. Many of the alterations are of small magnitude and may not be of consequence to most persons under treatment. Nevertheless, the consistency of research reports on such findings rejects the implication that they be ignored. What is the long-term significance of abnormal glucose-tolerance curves, elevations of the level of certain plasma proteins, altered serum lipids? And, if we do not know, what courses can we plan, and what alternatives do we have?

I am mindful of the urgent need for new and better contraceptives and of the considerable impact on our society if the oral contraceptives are no longer available. I am also mindful, however, of potential hazards if we proceed incautiously without adequate knowledge. Faced with this dilemma, whereby we can neither proceed with unlimited use of the drugs nor discontinue their use without obvious and pressing reason, I urge the promulgation of an intermediate course based upon a broad program of basic, clinical, and epidemiological research into the immediate and long-range effects of the contraceptive steroids.