Drill and Calhoun have structured their report on a study whose authors, in effect, say, Don't use this for an evaluation of thrombophlebitis. The reader should have been forewarned. The physician who depended on the Drill-Calhoun report and simultaneous AMA editorial would not be aware of this fundamental discrepancy. To be aware, he would have had to search for the unpublished study or read the FDA report.

Mr. GORDON. Doctor, may I interrupt for a moment. Let me read from the FDA report on this study. This is on page 29:

> It is our opinion that the evidence presented by Drill and Calhoun which constitutes the main negative evidence published to date is inadequate to show that the incidence of thromboembolism is either unaffected or reduced by oral contraceptives.

Now, what, in your opinion, has been the effect of this Drill-Calhoun report, who were, as you say, employees of a pharmaceutical firm?

Dr. KASSOUF. I think you must go back to that point in time in September 1968. A physician, if he read the British journals, was told in 1967 and 1968 that the pill does kill. It does cause pulmonary embolism. However, that was neutralized by the explanatory statement—mentioned before—by FDA that it might not be applicable to us.

So, therefore, the average American physician, as late as 1968, could, with assurance, tell his patient, if he was unaware of the British work, that the pill is absolutely safe. This would be a disservice to his patient, and is not consistent with the majority of opinion today.

I think the physicians deserve better than this report as the lead article in the AMA. This journal carries much of the advertising. The AMA editorial made no criticism of this Drill-Calhoun paper which would advise the reader as to what the weight of the evidence was. Was the British work more substantial or was it not. They merely pointed out there seems to be a difference of opinion.

Mr. DUFFY. Doctor, does this quote say that the Drill-Calhoun study is wrong? I have read it three or four times.

Dr. KASSOUF. No——

Mr. DUFFY. It says it is inadequate.

Dr. KASSOUF. To prove their conclusion.

Mr. DUFFY. It does not say it is wrong. It just leaves the question unanswered because the study is inadequate.

Dr. KASSOUF. I think in one sense it is wrong in that they drew a conclusion from these statistics, and FDA is saying very clearly that the statistics they used are inadequate to justify their conclusions. I do not know what you call that, but it's not consistent with the data they used.

The conclusion is not consistent with their own data. What I am saying is the American physician deserves a little better treatment than to have this Puerto Rican data presented to them now which was not presented to them in 1962, to have an unpublished study presented to them. In fact, I am a pill watcher, but I never went back to track down the unpublished report. I agree wholeheartedly it is not actually a report. I found it with some difficulty. It is a press release. I think I have it here.

This is the unpublished study, and it is labeled a news release by Planned Parenthood World Population. It is not a formal article, and

I think it raises a question. I am sure Dr. Guttmacher, if he felt in 1965 he had solid evidence that the pill was not related to thromboembolism, Dr. Guttmacher, who has an excellent reputation, would have published it. Thrombophlebitis has been an issue since 1961, and 1962. But it has never been published in the journals, so far as I know.[1]

So why was it used in the Drill-Calhoun report? I can only raise the question.

Mr. DUFFY. Maybe that is the reason the FDA felt that the evidence presented by Drill-Calhoun was inadequate, which is all the quote says.

Dr. KASSOUF. The study is inadequate, not because it is unpublished, but for other reasons and we do not have time to go into these statistics. Dr. Guttmacher, there is no better authority on the study than the author, states it is inadequate to deal with the question of thrombophlebitis. This study was not designed to provide a comparative incidence of thrombophlebitis. But the average physician who has a lot of trouble keeping up with the literature certainly could not go back to that unpublished study. I had trouble getting it.

So the point is, in 1968 the average American physician had good reason to believe, there was no link between the pill and phlebitis. This is in spite of two prior, British reports.

Senator MCINTYRE. Doctor, I take it you have more than one copy of the so-called Puerto Rico report?

Dr. KASSOUF. Of the original study. I have it here and you may have it.

Senator MCINTYRE. Would you like to submit that for the record?

Dr. KASSOUF. Yes, certainly.

Senator MCINTYRE. Without objection, it will be included in the record.[2]

Dr. KASSOUF. The AMA has a puzzling record in regard to the pill. In 1962 a professor of ophthalmology submitted a case report involving stroke. The AMA refused to publish it because of certain controversies. The paper was finally submitted to the FDA, and the FDA was unwilling——

Mr. DUFFY. Are you aware of what these controversies are?

Dr. KASSOUF. No. FDA was not willing to give me the information.

Mr. DUFFY. You say there were certain controversies but you do not know what they were.

Dr. KASSOUF. Between the author and AMA.

Mr. DUFFY. Do you have reason to suspect that these controversies may have actually touched on the merits of the article or whether the articles submitted to be published were worthy of publication?

Dr. KASSOUF. Well, I don't know.

Mr. DUFFY. Yes or no. You don't know the controversy?

Dr. KASSOUF. I do not know the details of the controversy. This is the total information I have at the time I testified to Senator Gruening.

Mr. DUFFY. For all we know, these controversies could have involved the payment of a fee and may have had nothing to do with the scientific validity of the report; isn't that correct?

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[1] The news release entitled "Mass Oral Contraceptive Study Findings Released," appears in Oral Contraceptives—Volume Three—Appendixes.

[2] See p. 6127.

Dr. KASSOUF. That is unlikely, but if it were printed we would have been alerted to this problem in this country a lot sooner than we were.

Stroke problems originated in Great Britain. So I think someone might look into the problem of why the AMA did not publish this. I think it would be very important. We seem to follow the British by 2, 3, and 4 years in finding out about side effects.

FDA is unwilling to reveal any other details. In March 1963 the AMA Council of Drugs reviewed Enovid. It omitted mention of thromboembolism under precaution, and the drug was under precaution at that time. Since the Drill-Calhoun paper represents a major policy statement by the manufacturer one would perhaps expect extraordinary standards by the AMA in regard to excellence, reliability, and full disclosure.

This brings up the question of the now well-known report by Dr. H. Dubrow and Dr. M. Melamed, entitled, "Prevalence rates of uterine cervical carcinoma in situ for women using the diaphragm or contraceptive oral steroids." According to the Medical Tribune, this paper was refused publication by the AMA except by the condition of extensive revision and editorial criticism. After many months the authors withdrew the paper and submitted it to the British Medical Journal where it was quickly published. The fact the British published it speaks for its viability. The fact Dr. Roy Hertz discussed the paper in the FDA report adds evidence to its importance.

I believe it is evident that for a physician to be reasonably well informed he will have to read other American journals, unpublished studies, and FDA reports. All this would not be enough unless he read the British journals. In the end it is the patient who takes the risk. The last bit of information she is apt to receive from the doctor's office or clinic is in the form of pamphlets produced by the contraceptive manufacturer. The samples I brought are all in circulation. None have ever been recalled by the manufacturer or FDA.

A few excerpts will illustrate the problems. A 1967 pamphlet by Ortho-Pharmaceutical is entitled, "A Woman's Guide to the Methods of Postponing or Preventing Pregnancy."

Mr. GORDON. Do you have it there? Could you hold it up?

Dr. KASSOUF. Yes. Here it is. It discusses the IUD and the pill. The introduction states:

> The first consideration obviously is safety. The ideal method of preventing pregnancy must be one that is harmless to use. None of the methods mentioned in this book is harmful to a woman in normal health.

This is untruthful and dangerous advice.

Another, entitled, "Planning Your Family," copyright 1966, by G. D. Searle & Co., responds to a question concerning long-term safety of the pill. In part, it answers:

> There is no evidence that Ovulen interferes with nature to any extent greater than repeated pregnancies * * *"

It concludes the answer with:

> The effects of birth control pills have been studied, possibly, more thoroughly and for a longer continuous time in the same persons and in more women than any other drug. Evidence of their safety and effectiveness has been continuously confirmed.

Mr. DUFFY. Excuse me, Doctor, but just a casual reading of the FDA conclusions might indicate that that last sentence is still correct. Are you suggesting to us that the statement is not correct?

Dr. KASSOUF. I think I submitted evidence that this is, perhaps, not the best tested and certainly not the best reported drug. That is in my experience as a practitioner.

I do not think the FDA report says anything about birth control interfering with nature to any extent less than repeated pregnancies.

Mr. DUFFY. Maybe I was not specific.

Dr. KASSOUF. I am sure that that is a fact.

Mr. DUFFY. I was confining my remarks to the last sentence.

Dr. KASSOUF. The fact that the FDA report comes in 9 years later means to me these pills have not been studied more thoroughly than other drugs, and in addition evidence of their safety and effectiveness is not what the FDA report found.

If one reads the report and not the conclusion, one must disagree wholeheartedly with that legal statement. I am always suspicious when doctors make a legal statement. The conclusion said that they designated it legally safe. Why don't they make a medical judgment? In the report itself a death risk was documented and a risk of pulmonary embolism confirmed.

Mr. DUFFY. Would you agree with me, though, that the report—remember I am not a doctor and I cannot read this report the way you would, but I certainly can read the section of that report that gives the conclusion and that section says all things considered, the pill is safe.

Dr. KASSOUF. Of course you read what you want to read.

Mr. DUFFY. If you read your last sentence, which was the one I am asking you about it says "* * * evidence of their safety and effectiveness has been continuously confirmed." This was published in 1966. In 1969 FDA says the pill is still safe.

Dr. KASSOUF. But it is still in circulation. If you read the FDA conclusion, you have one leg to stand on. If you read the rest of the report you have two legs to stand on, and if you read the report you will find a definite risk of clotting was established.

I do not interpret these two events in the same manner as you do, that evidence of their safety and effectiveness has been continuously confirmed. I think the FDA report tells us this after 9 years of concern. This particular committee has been at it 2 to 3 years, and finally they confirmed a risk. I do not think they found safety, they found a risk. This is how I interpret it.

If the patient asked me what did the 1969 FDA report find, I would have to tell them it found evidence of pill injury.

Mr. DUFFY. This will engage us, of course, in a discussion of what safety means, but I think the report did say that all things in balance, benefit versus risk, the pill is safe.

Dr. KASSOUF. I heard that discussion this morning, but everyone conveniently left need out of the benefit-risk ratio. Chloromycetin has a tremendous benefit-risk ratio, but I suggest you do not take it unless you desperately need it. Until you put need in that ratio, that conclusion is meaningless.

One other thing about that was discussed in the conclusion. It seemed convenient to invoke the idea of universal toxicity about drugs.

All drugs cannot be absolutely safe, is what was said in that conclusion, and that is not my experience.

Of course, if we are talking about a sore arm or minor reaction from a drug, that would be true. But I am talking about deaths. We do have important and significant drugs on the market today that are used by millions. As of 10 days ago, I bothered to check with the manufacturer, and was told there were no reported deaths. So I do not think you can raise the umbrella of universal toxicity over this problem and say all drugs have serious side effects and, therefore, the birth control pill has some and conclude it is OK.

Mr. DUFFY. Well, Doctor, you just told me now that in some drugs you are going to go check with the manufacturer when they tell you there are no drug related deaths.

Dr. KASSOUF. Reported to them.

Mr. DUFFY. I didn't hear that.

Dr. KASSOUF. Reported to them.

Mr. DUFFY. You have told us before you cannot believe the manufacturer in some instances. But here you will. I don't understand.

Dr. KASSOUF. It depends on the manufacturer.

Mr. DUFFY. Let me find out what sort of research you yourself have done in these areas to determine some of these questions.

Dr. KASSOUF. Please clarify the question.

Mr. DUFFY. Have you researched any of these questions associated with the pill or are you relying strictly on what may be reported by others?

Dr. KASSOUF. What question are you referring to.

Mr. DUFFY. Well, we were talking a moment ago about the universal toxicity of drugs.

Dr. KASSOUF. Yes.

Mr. DUFFY. You have. What sort of research studies have you conducted which would lead you to draw conclusions about the universal toxicity of drugs?

Dr. KASSOUF. I am not a researcher. I am a practitioner. I could not find a death reported in the literature due to mumps vaccine.

Mr. DUFFY. Do I understand you have not done any research in any area?

Dr. KASSOUF. It depends on what you mean. The fact that I left my practice to go to the library and look and the fact that I took the trouble to check with the manufacturer, is research on a very small scale. It was an inquiry.

Mr. DUFFY. You do not deal with large numbers of patients under controlled conditions?

Dr. KASSOUF. I deal with ——

Mr. DUFFY. With reference to a particular problem; is that correct?

Dr. KASSOUF. Under controlled conditions?

The question is vague. I would like to answer it if you would clarify it. I did not run any study on the mumps vaccine, if that is what you are asking. I take issue with the idea, however, that there is or always will be such a thing as universal toxicity.

Mr. GORDON. What do you mean by universal toxicity?

Dr. KASSOUF. They said in the Hellman report—that no drug can be absolutely safe.

Mr. GORDON. Absolutely safe?

Dr. KASSOUF. Yes. Well, I do not think we should bother minor reactions or little irritations in this kind of a discussion. If you want to include those small events as issues of safety, then I have to withdraw my argument. But I am talking about serious reactions.

Mr. GORDON. You could run this into the ground, too. If it causes a headache, it could still be safe.

Dr. KASSOUF. Yes.

Mr. GORDON. What you are saying, as I understand it, is you have to be selective about this. Some cause death, aplastic anemia, thromboembolism, which is serious to the body, serious illness.

Dr. KASSOUF. I would say, perhaps, it is a disservice to give the public the idea that every drug has lethal effect or can have a lethal effect. I do not think the experience to date justifies that.

Now, perhaps, someone will be able to tell me about a death with the mumps vaccine, and I will retract the statement.

Mr. DUFFY. Doctor, let me just return to my original premise. My understanding is, then, that you are a practicing physician.

Dr. KASSOUF. Yes, sir.

Mr. DUFFY. What type of practice?

Dr. KASSOUF. Internal medicine.

Mr. DUFFY. You did not conduct research in any type or form?

Dr. KASSOUF. No, sir; it is hard enough to keep up my practice.

Mr. DUFFY. Is it my understanding that the members of the FDA committee who concluded that the pill was safe, were men who are research-oriented, they are not practicing physicians in the sense you are a practicing physician, these are men who have actually gone out and studied the problem under controlled clinical conditions with large numbers of patients and have specifically dealt with the problems associated with the pill for long periods of time?

Dr. KASSOUF. Some of them are academic physicians, yes. I cannot give you the number.

Mr. DUFFY. And you say it is their conclusion, as people who have gone about, actually firsthand, to study this problem——

Mr. GORDON. Not every one of them.

Senator MCINTYRE. Go ahead. Proceed.

Mr. DUFFY. It is their conclusion that the pill is safe.

Now, you are a practicing physician, having done no research; would you challenge their admitted expertise?

Dr. KASSOUF. I read their report.

Mr. DUFFY. So you feel that that is a substitute for research in this particular case?

Dr. KASSOUF. No. I think it is a reason to contest their decision. In their report they found a risk. They did not find safety. In 1969, for the first time, they have documented a risk and the conclusion is that it is safe. I think that is hard for me to understand.

Now, maybe the others understand it, but I do not.

Mr. DUFFY. In other words, really what you are saying is you cannot understand the conclusion and, therefore, you will not accept it.

Dr. KASSOUF. Well, accepting or rejecting the conclusion really is not the total issue. We are debating, I presume, the meaning of their studies.

Senator McINTYRE. Proceed, Doctor.

Dr. KASSOUF. To go back to this for a moment, "Evidence of their safety and effectiveness has been continuously confirmed."

I will put the safety issue aside for the moment. The reader may ask if what the pamphlet said was so, why have drug dosages been frequently revised. The original pill had its dosage revised generally downward on two occasions after release to the public.

The last revision was upward in the estrogen content. It is clear that the minimum effective dose had not been established and therefore overdosage resulted. The last revision on estrogen is contrary to recent press reports of British research which states estrogen is best reduced. The safety issue seems to grow while minimal ideal dosage seems yet to be established.

In answer to a question, can the pill cause cancer in women, the answer was, "To date, no causal relationship between the use of oral contraceptives and cancer has been established." The last FDA conclusion states its answer in more complete form, i.e., "potential carcinogenicity of the oral contraceptives can be neither affirmed nor excluded at this time."

The Parke-Davis pamphlet dated June 1969 answers a question about clotting. The answer:

> Although such disorders are rare and may be experienced by any woman, studies in Great Britain indicate they may occur more often in women using these drugs.

Four years of British research undone by one word. The British stated the pills do cause clotting and then gave the numbers.

Lastly, a pamphlet entitled "After Your Doctor Prescribes Ortho-Novum", copyright 1968, admits to the vascular problem on page 16 and gives some generally good advice. On page 18 it is all undone. The question, "Can any woman take Ortho-Novum tablets?" The answer was, "Any woman who is in good health and not pregnant will find Ortho-Novum safe and effective when taken as directed."

This is enough to demonstrate known hazards are denied and distorted. Major concerns are casually treated or ignored. Some of the pamphlets mislead and misinform, others are frankly dangerous, but all have one thing in common—they all seem to disparage the reader's right to know.

Encouraged by the pamphlets and the silence of organized medicine and Government, the drug companies extended their corporate reach. On January 2, 1969, Christopher Lehman-Haupt of New York Times reviewed negatively, "The Doctor's Case Against The Pill," by Barbara Seaman. He concluded his review with, "One wonders why the drug companies have been so exercised by it. In a way, their attempts to warn book reviewers against it are more disturbing than the book itself." Mr. Lehman-Haupt has performed a public service in exposing the drug companies' attempts.

The cross currents of information to the physician are bewildering. FDA cautioned about British data in 1968, but did not warn in regard to the manufacturers' policy statement. That appeared in the Journal of the American Medical Association. In 1969, the FDA confirmed the British findings of risk and, at the same time, found the manufacturers' statement wanting.

The 1969 FDA report is available, but not easily accessible to the average physician. It is going on 5 months since the last FDA report and the profession has received no official statement of the findings. Now, new information comes from Great Britain. Physicians in Great Britain have been warned against pills with high estrogen levels. FDA is unwilling to issue such a warning here to date, although their own data points in the same direction. An advisory can be withdrawn—but high dose pill injuries that may occur in the meantime cannot.

Press releases state that the British results will take 2 to 3 months to make the raw data available for release, thus thwarting FDA attempts to examine the data, as far as the United States is concerned. When the British released their first preliminary data we refused to act for over 1 year, and then when we did, we neutralized the warning.

Finally, "full disclosure" to the patient is desirable and morally necessary as the pill represents a mass experiment. Full disclosure should not become an escape device, placing final responsibility for using the pill upon the patient. Many women are unequipped by experience or temperament to make this difficult assessment.

While the experiment continues, it would be prudent to acknowledge both the known and unknown risks by reducing total exposure to these steroids. This can be done, in large part, without interfering with private or public population problems. Simply stated, the pill should not be recommended for women who have not completed their families.

This is the one group where the contraceptive risk cannot be substituted for a pregnancy risk but must be added to it.

Senator McINTYRE. Doctor, if I may make a reference to the fact this morning a difference arose between the task force report headed, I believe, by Dr. Hertz and the Chairman's overall summary. It seemed to some of us there was an inconsistency in the fact that, as a task force chairman he, at least, approved the summary of Dr. Hellman.

This has caused us, the Chairman here, the Senator from Wisconsin, has indicated that he really does not know what is meant by the word "safe" within the intent of the legislation, which was the term used in the Chairman's overall summarizing of the report.

I am informed that Dr. Hellman will eventually be a witness before the committee, so I think we will all get a chance to find out what is meant by "safe" as opposed to "safe within the intent of the legislation," if there is any difference.

So I can appreciate Mr. Duffy's and your difficulty in trying to get straight on that.

Doctor, you seem to be taking the position that if the pill remains on the market it should be reserved for women who had completed their families. Is that a correct interpretation and, if so, why did you think it should be reserved for this group of women?

Dr. KASSOUF. That is in general. That will not solve everybody's need for the pill. I think it is evident now from what we have heard, so far it would be wiser to reduce the experiment rather than to enlarge it. There seems to be a big cloud hanging over the pill in the form of cancer and in the form of metabolic disorders. The experts have told us it is going to be many years before we have an indication if it is so or not.

I think it would be prudent for those who do not have a real need, and overriding need, to use one of the more conventional methods.

At the same time, this would remove, for instance, the young bride whose fertility has not been established, as Dr. Whitelaw spoke of yesterday. That would be one group that would be eliminated by this recommendation. That is not an insubstantial group. I understand something like 7 or 8 percent of marriages are sterile for one reason or another.

If that particular young bride takes the pill she has no possible chance of gaining. She has made a bad bet. She has nothing to gain because fertility has not been established.

We are in fact talking more of birth spacing.

Senator McINTYRE. Go ahead, finish your answer.

Dr. KASSOUF. This is the group who have not completed their family. I think birth spacing is, perhaps, more apropos than birth control, and to achieve birth spacing we have methods that are 90, 95, 98 percent effective and carry no risk.

If they need the high-level effectiveness of the pill, and another child would be a catastrophe, I think I might go along with that. I do not prescribe the pill. These are some of my suggestions as a pillwatcher.

Senator McINTYRE. As a practicing physician, in your opinion, for a woman who has definitely decided that she has completed her family, would it not, perhaps, be safer to undergo sterilization than to continue taking the pill for the remainder of her fertile years, in your opinion?

Dr. KASSOUF. In my opinion, I would do certainly something else. Either an IUD or perhaps consider sterlization of the woman or husband. That is more reasonable than taking these hormones, let us say, for the next 20, 25 years.

Senator McINTYRE. I take it, Doctor, from your statement and your testimony here, that you are most unhappy about the way the pill has been handled by the FDA, by the pharmaceutical industry and by the medical profession itself; is that right?

Dr. KASSOUF. I think the record shows that. It is 9 years since we have come in with the demonstration of risk. The question arose in 1962 but not answered till 1969, and the British got there ahead of us. I think there are a lot of questions as to how did it all happen that way.

Senator McINTYRE. And lastly, Doctor, you say in your last sentence that while further studies of the pill are being conducted total exposure to these drugs should be reduced by not recommending the pill for women who have not completed their families.

How could this reduction be accomplished, and if such a recommendation were placed in the labeling for the pill, do you think most physicians would abide by it?

Dr. KASSOUF. I think they very well may. We follow recommendations in regard to other drugs. One that comes to mind, for instance, is Indocin. I believe under indications, there is a full discussion. I cannot quote it, exactly but it is suggested the patient should probably be treated by aspirin, by physiotherapy before using this powerful drug. No such discussion appears on the pill labeling under indications. I think it says something to the effect, for fertility control or ovulation control, period.

I think if there were a discussion physicians would have to think about it. In fact, there might be a legal question if the pill is the first

choice contraceptive. I think there should be an attempt at other methods; either rhythm, contraception, diaphragm, jellies, for the worst that will happen to her is she might have a baby a few months sooner. That is not the biggest catastrophe a married couple will run into in their lifetime.

Senator McINTYRE. Any further questions?

Mr. Duffy.

Mr. DUFFY. Yes, I have several.

Mr. GORDON. Doctor, you pointed out some difficulties in physicians getting complete and current information. What would you recommend be done in this field?

Dr. KASSOUF. It is a complicated question. I think there is no simple answer. But looking back over the 9 years, I think it is clear FDA has inherited the safety question by default. The companies did not pursue it. Organized medicine did not do it. The reports we find now are Government-sponsored both in Britain and in the United States.

It would mean to me, one of the answers would be to expand and build and support our FDA to a much greater extent than we have done in the past.

Mr. GORDON. Thank you.

Mr. DUFFY. Doctor, in your practice, how many people a year do you treat?

Dr. KASSOUF. How many people?

Mr. DUFFY. How many people a year do you treat in your practice?

Dr. KASSOUF. I have never kept the score, but I guess maybe——

Mr. DUFFY. Can you give me an answer?

Dr. KASSOUF. I guess maybe I see a hundred a week, maybe more, maybe less.

Mr. DUFFY. A hundred a week. How many of these are women?

Dr. KASSOUF. I practice internal medicine and I would have to make a guess that probably a little more than 50 percent are women.

Mr. DUFFY. For the sake of argument, may we say 50 percent are women?

Dr. KASSOUF. I am unprepared, really, to give you a factual answer. We will call it a guess.

Mr. DUFFY. That would be 50 women a week, approximately?

Dr. KASSOUF. Maybe. There are some youngsters.

Mr. DUFFY. Of these 50 women a week that you see, how many are using oral contraceptives?

Dr. KASSOUF. I never kept a score.

Mr. DUFFY. Can you give me an estimate on that?

Dr. KASSOUF. I really could not. I have not brought a record.

Mr. DUFFY. Ten percent, 20 percent?

Dr. KASSOUF. There is no point in my guessing. It could be 90 percent as far as I know.

Mr. DUFFY. You have never asked them?

Dr. KASSOUF. I do ask them when the symptoms come up that suggest to me there may be a relationship between a drug and their symptoms.

Mr. DUFFY. But unless there is such a symptom, you do not ask them and, therefore, you do not know?

Dr. KASSOUF. We usually ask what medication they are on, but I

just came unprepared for that. I would have to tabulate all the drugs that they take.

Mr. DUFFY. Do you regularly prescribe contraceptive drugs?

Dr. KASSOUF. No, I never have. I am in group practice, and we have two gynecologists in the building, and for that reason they have always done that.

Mr. DUFFY. You say you have never done research yourself, but have you read, for instance, the work of Corfman and Seigel which has been mentioned by the previous witnesses today?

Dr. KASSOUF. In the FDA report?

Mr. DUFFY. No; Dr. Corfman and Dr. Seigel recently published a paper in JAMA which set out populations of patients needed in order to conduct statistically valid experiments. Are you familiar with their work?

Dr. KASSOUF. I am not familiar with that article at the moment. Maybe when I see it——

Mr. DUFFY. It was published in 1968.

Dr. KASSOUF. I do not recall it.

Mr. DUFFY. It was an article that several of our previous witnesses referred to or alluded to. As a matter of fact, today Dr. Hertz and Dr. Kistner and also Dr. Bole made reference to that article.

Now, it seems difficult for me to understand how you feel that you, not having done research and not being familiar with a very basic work in this field—a work that one must be familiar with in order to do research or even to analyze the results of research well—would be able to look at any research study and determine that the research was done properly, that the patient populations were sufficiently large to have a statistically valid result.

Dr. KASSOUF. Experimental design is certainly a problem and in the past on several problems I have sought help, as I did when we had this disagreement with the Wright Committee. But if you are asking me whether I——

Mr. DUFFY. Did you say it was difficult—wasn't it your answer that it was difficult, for you to look at a published article and determine whether the research had been properly done?

Dr. KASSOUF. I think most physicians would have to admit nowadays the articles are quite complicated.

Mr. DUFFY. Particularly for one not having done research.

Dr. KASSOUF. I do not think it has to do with that alone, but that depends on your training in biostatistics and epidemiology.

I had suggested we have become more dependent on FDA. The Drill-Calhoun paper had only one series large enough to test the hypothesis. This series was disqualified by FDA. I do not think the average practitioner would realize that. You would have to be a mathematical expert. I know if you are testing for reaction in 1,000 or 2,000 and test a series of 850 people in Puerto Rico you are probably going to miss it.

Mr. DUFFY. Let me ask you another question, Doctor.

Have you read any book or any recognized work on how to conduct research?

Dr. KASSOUF. I have read articles in that regard.

Mr. DUFFY. On how to conduct research? Would you recall any of these articles that you read?

Dr. KASSOUF. No, not at the moment.

Mr. DUFFY. Doctor, would it be fair to say that you really are not too certain whether you do know how to conduct medical research?

Dr. KASSOUF. I came here telling you I am a practitioner, not a researcher. I did not misrepresent myself.

Mr. DUFFY. I would submit, therefore, that the man who really does not know how to conduct research may not be fully capable of interpreting it. He may agree with the conclusions stated.

Dr. KASSOUF. You may be right. However, when sudden deaths occur in an experimental series—and there is not a physician I have talked to, researcher or not, who said these should not have been reported to the FDA. That may have nothing to do with the academic training. It may be just commonsense.

Mr. DUFFY. Let us pass over that question because I think I have made my point there.

The British studies that you allude to, have you seen the supporting data for these studies or are you only advised as to what the conclusions are?

Dr. KASSOUF. No. Most of us have just seen the press reports.

Mr. DUFFY. You have merely seen the press reports. but it appears you accept their conclusions.

Dr. KASSOUF. Well, you know in medicine you have got to have confidence in certain bodies, and I think over the years, we found the companies stating that estrogen is not dangerous, and the British saying it is. What is the alternative?

Mr. DUFFY. But you are willing to accept these studies never having seen the underlying data.

Dr. KASSOUF. I am willing to accept the British conclusion. There is no reason for not cutting back to the lowest dosage as they are equally effective. If studies next year show the British are wrong, the advisory can be withdrawn, but vice versa, patients who are injured cannot have their injuries withdrawn.

Mr. DUFFY. All I can say, Doctor, to be very willing to accept the conclusions of a study without even having access to the fundamental supporting data is a very interesting way to do research.

Dr. KASSOUF. I am willing to accept it to make a clinical judgment on that basis. The alternative we accept here is to use drugs that are equally effective.

I will ask you, what would be the rationale for continuing to use the high-dose tablet if there is a fear that it is causing these injuries in greater incidence, when both the high and low dose are equally effective? I do not think there is any alternative but to start using the low-dosage tablet. Why should one wait until the patient or the British provide incontrovertible proof of injury? We do not have to do that in medicine.

We do not have to wait for incontrovertible proof. We have waited too long if we do that in this instance.

Why mistrust the British is another question? We usually confirm their results. The drug companies still say there is no risk or at least one of them does.

Mr. DUFFY. Doctor, I am not prepared to say that anybody is right or anybody is wrong. But even if I had access to the fundamental

supporting data for these conclusions, I would not know what to do with it. I could not evaluate whether the research is properly done or whether the conclusions drawn from that research are valid conclusions. I am not a skilled medical technician, so I just would not know what to do with it.

But certainly I know from other areas that one should be very leery about accepting conclusions without understanding the processes that one must use to reach those conclusions.

Dr. KASSOUF. You do not have the responsibility of a patient's life, and we do, and given these circumstances of equal effective drugs, I think it is wrong to wait even for FDA advisories.

I think physicians who have read the press reports have sufficient reasons to back away from the high-dose tablets.

Mr. DUFFY. Thank you very much.

Senator MCINTYRE. Thank you very much, Dr. Kassouf, for coming here this afternoon, this morning, too, and testifying.

The committee is always very glad to hear from those men who are down in the field working with the problem every day, and I am sure Mr. Duffy realizes that, too.

The committee will stand in recess until Wednesday, January 21. We will meet in room 2221 at 9 : 30 a.m.

(The document above-referred to, follows:)

[From the Journal of the American Medical Women's Association, Volume 17, Number 10, pp. 797–802]

CONCEPTION CONTROL WITH NORETHYNODREL—PROGRESS REPORT OF A FOUR-YEAR FIELD STUDY AT HUMACAO, PUERTO RICO

(Adaline Pendleton Satterthwaite, M.D., and Clarence J. Gamble, M.D.)

In 1937 sterilization was legalized in Puerto Rico for socioeconomic as well as medical reasons, and this has become the most popular permanent solution to the high fertility rate on the island. However, numerous requests from mothers coming to the Ryder Memorial Hospital in Humacao, Puerto Rico, led us to look for an effective but reversible method of family planning. For practical use, such a method must be safe and acceptable, simple enough to be understood by the uneducated person, and as inexpensive as possible. Since 1956 there have been reports of certain 19-nor-progestational steroids which, on oral administration, inhibit ovulation. The two compounds which have reached commercial production and which have been most frequently studied are norethynodrel* and 19-norethisterone (norethindrone).†

Dr. Satterthwaite was chief of the Department of Obstetrics and Gynecology at the Ryder Memorial Hospital, Humacao, Puerto Rico. She now directs the research program and family planning clinic at the same hospital.

Dr. Gamble is associated with the Population Studies Unit of the Harvard School of Public Health and director the Pathfinder Fund.

In April, 1957, a field study of oral contraception with norethynodrel was, accordingly, begun under the joint direction of the Population Studies Unit of the Harvard School of Public Health, Boston, and the Ryder Memorial Hospital. From the first 3 years of experience it was concluded that norethynodrel is acceptable, safe, and effective and does not prevent subsequent pregnancies (1–11). A further experience of 20 months has led to a second review of the users, the results of which are presented herewith. In this study we have been particularly interested in those patients who have continued the medication for 3 years or more. Those who have discontinued norethynodrel for one reason or another and continued at risk of pregnancy have been followed post partum and the babies

*Envoid, G. D. Searle and Company, who supplied the tablets used in this study.
†Norlutin, Syntex and Parke-Davis, Ortho-Novum, Ortho Research Foundation.

NOTE.—Numbered references at end of article.

have been examined when possible. The results of reexamination of the long-term users (there are 91 women with 40 or more treatment cycles), including the endometrial biopsies, Papanicolaou smears, cervical biopsies, and laboratory analyses, will be presented at a later date.

POPULATION CHARACTERISTICS AND PROCEDURES

Women, many of them post partum, were admitted to the study from the Ryder Hospital outpatient department. Some were enlisted in their homes. Women under 40 years of age, of demonstrated fertility (having had two or more living children), and living with a sexual partner were eligible for inclusion. The average characteristics of the 838 women who used the method for a month or more are given in table I. These women averaged 5 pregnancies each, a rate of 61 per 100 couples per year of married life. After deducting 10 months for each full term delivery and four months for each abortion the rate of pregnancy was 117 per year of exposure. The average interval between pregnancies had been 20 months.

After preliminary pelvic examination those women with lactation amenorrhea received a bottle of 20 pills to be started immediately. The other patients were instructed to return to the clinic while menstruating to start the pills on the fifth day of the cycle, to be completed on the twenty-fourth day. It was emphasized that the pills must be taken daily and that if one was forgotten two should be taken the following day. Withdrawal uterine bleeding usually occurred 2 to 4 days after the last pill. The users were instructed to return with the "menses" each month to start a new series of pills on the fifth day of the cycle. In the absence of withdrawal bleeding the pills were to be restarted 8 days after the last pill had been taken. Some of the patients have been followed in their homes by monthly visits of the social worker. Patients wo had used the pills without difficulty for several months were often given two months supply.

TABLE I.—POPULATION CHARACTERISTICS AT START OF STUDY

Number of women	838
Age range	16–46
Average age	26.9
Average years married	8.2
Pregnancies (averages):	
Children now alive	4.2
Born alive but died	.4
Stillborn	.05
Abortions	.34
Total pregnancies	5.0
Pregnancies per 100 married years	61
Pregnancies per 100 years of exposure[1]	117

[1] "Years of exposure" are the total years married less 10 months for each full-term delivery and 4 months for each abortion. Periods of separation though appreciable for a few families was not enough for the whole to warrant consideration in the calculation.

$$\text{Rate} = \frac{\text{Total number of conceptions} \times 1{,}200}{\text{Total months of exposure}}$$

TABLE II.—SUMMARY OF EXPERIENCE

	Total	Active users	Discontinued
Number women	838	395	443
Treatment cycles—all doses	15,150	10,472	4,778
10 mg	3,947	----	----
5 mg	10,498	----	----
2.5 mg	705	----	----
Woman-years	1,165	----	----

For the first two years we used 9.85 mg. of norethynodrel with 0.15 mg. of the synthetic estrin, ethynyl estradiol-3-methyl ether. In the spring of 1959 the dose was reduced to 5 mg. and 0.075 mg. of the two compounds respectively. In the fall of 1960 we began to give new patients 2.5 mg. and 0.1 mg. of the two. These reductions in dosage were designed to reduce the expense and the side effects without impairing the effectiveness.

RESULTS

The 838 women used norethynodrel for 1 to 62 treatment cycles, from 1 to 54 months (4½ years). There were a total of 15,150 treatment cycles or 1,165 woman years of experience (Table II). While 53 per cent of all users discontinued the method for a variety of reasons (Table III) only 147 (17.5 per cent) did so for reasons inherent in the method, or one such discontinuance in 8 woman years of use. The other reasons given, such as moving, separation, or husband's objection appear unrelated to acceptability.

The reasons for withdrawal of the 443 patients are given in table III. Ninety-nine patients were sterilized. We lost 115 patients who moved somewhere else on the island or to the continental United States. Nine are in the menopausal period and 10 have died. Six of the latter were victims of the Humacao flood, one died of severe burns, two died of "heart attacks," and one of subarachnoid hemorrhage. However, 42 patients who dropped out for various reasons (the most common being the absence of the husband in the United States) have restarted. Thirteen of these have discontinued for the second time.

The greatest number of withdrawals, one sixth of all users, was due to unpleasant side effects. One fourth of the patients discontinuing did so in the first 5 cycles (Table IV). Several patients who withdrew for reactions after 30 or more cycles appear to be approaching the menopause. Vaginal cytology studies of these patients are to be made more closely to try to determine whether there is any estrogen deficiency.

TABLE III.—REPORTED REASONS FOR DISCONTINUING NORETHYNODREL

Reasons	Number of persons reporting each reason	Percent of all users
Inherent in the individual	306	36.6
Moved away (53 to New York City)	66	8.0
Persons who have not returned—living too far to revisit	49	5.8
Separated or widowed, (37 husbands to United States)	64	7.6
Sterilized [1]	32	3.8
Found to be pregnant	25	3.0
Pregnant when started medication	12	
Pregnant because of incorrect use	13	
To get pregnant	37	4.4
Menopause	9	1.0
Died (6 flood victims)	10	1.3
Medical reasons (concurrent illness)	8	1.0
Inability to follow instructions	6	.7
Inherent in the community	83	9.9
Frightened by rumors	36	4.3
Difficulty in securing supplies (working, children sick)	11	1.3
Advice of private physician (usually because of some "reaction")	16	1.9
Religious aversion	13	1.6
Husband opposed to practice	7	.8
Inherent in method	147	17.5
Unpleasant side effects [2]	139	16.6
Tired of taking pills (1 was sterilized and 2 are again using pills)	3	.3
Not interested	5	.6
Totals:		
Reasons given	536	
Persons discontinuing	443	53.0

[1] 14 of these persons, originally planning to be sterilized, were persuaded to use norethynodrel in order that the effect of medication could be determined through ovairan biopsies during the salpingectomy operation. Another 67 withdrew for other reasons and became pregnant and had a subsequent sterilization post partum. 7 vasectomies were performed. In all 99 participants have been sterilized.

[2] There were 121 patients who mentioned side effects as the only reason for discontinuing norethynodrel. There were 18 others who mentioned side effects as one of several reasons, such as advice of private physician, husband opposed, or frightened by rumors. The 121 represents 14 percent of all users.

TABLE IV.—PERSONS DISCONTINUING MEDICATION; PREGNANCIES; PHYSICAL EXAMINATION OF BABIES BORN AFTER MEDICATION

Treatment cycles of use	Women using norethynodrel		After discontinuing norethynodrel					
			Discontinuing		Total pregnancies [1]	Babies		
	At start of period	Active now	Number	Percent		Born	Examined	Defects [2]
1 to 5	838	30	205	24.4	135	103	92	5
6 to 10	603	44	59	9.7	28	22	20	1
11 to 15	500	36	59	11.2	24	22	18	1
16 to 20	405	50	43	10.6	27	19	15	1
21 to 25	312	49	26	8.3	13	8	7	2
26 to 30	237	42	23	9.7	11	7	4	0
31 to 35	172	31	9	5.2	6	4	2	0
36 to 40	132	32	9	6.8	6	4	2	0
41 to 45	91	18	5	5.4	2	1	1	0
46 to 50	68	21	4	5.9	1	0	0	0
51 to 55	43	14	0	0	0	0	0	0
56 to 60	29	17	1	3.4	0	0	0	0
61 to 65	11	10	0	0	0	0	0	0
66 to 70	1	1	0	0	0	0	0	0
Total	395		443		253	190	161	10

[1] 169 women had 190 babies; 24 women aborted 25 times and 11 of the aborters also had full-term babies; 38 women are pregnant now.
[2] Defects: See discussion of each case in the notes.

NOTES ON TABLE IV

Defects and fetal loss:
5 (after 1 or 2 treatment cycles):
—Mother with chronic hypertension. 1st baby normal. 2nd Macerated 2 lb. fetus with missed premature labor
—Mother with chronic hypertension. 3 lb. premature infant who survived.
—Stillborn infant 7 lb. 14 oz. due to arrest of aftercoming head in breech delivery.
—7 lb. infant with congenital heart defect.
—Spontaneous rupture of pregnant uterus at term. 7 lb. 15 oz. stillborn.
1 (after 9 cycles of treatment):
—4 lb. premature infant born to mother with incompetent cervix. Neonatal death probably due to hyaline membrane.
1 (13 treatment cycles):
—Stillborn at term (7 lb. 8 oz.) due to untreated syphilis.
1 (18 treatment cycles):
—Term infant, cause of neonatal death unknown, according to medical certificate from the hospital where delivery occurred. Subsequent pregnancy terminated here with a full-term normal infant.
2 (23 and 24 treatment cycles):
—3 lb. 4 oz. premature with multiple congential defects associated with polyhydramnios. The mother has a strong family history of several sisters with children with multiple defects, although her other two children are normal.
—Full term female infant with port-wine stain on left thigh.
It seems unlikely that there is any relationship between the use of norethynodrel and fetal loss.

A study of the reasons given for discontinuing the drug reveals a delicate balance between the motivation of the woman on the one hand, with a desire to limit fecundity for physical or economic reasons; fears imposed by the community and the church; superstition and advice of the neighbors; and certain unpleasant but benign side effects that at least 44 per cent of women reported at the beginning of treatment. This is a typical comment of one country mother, 35 years old, with 8 children: "The pills make me feel as if I were a couple of months pregnant, but I wouldn't stop for anything because I don't want another child." A young clerk with 3 children who has used several of the conventional methods says she always feels a little "queasy" but because of greater security with the pills she will continue. At least half of the women, however, have no complaints.

No one who followed instructions became pregnant while using the medication. Twelve patients proved to be already pregnant when the treatment was started and 13 became pregnant due to incorrect use. Even if we should count the 13 as method failures, the pregnancy rate of 1 per 100 couples per year is far better than any other method reported in Puerto Rico (9). Among these 13 women who became pregnant were several long-term users who assumed that missing a few pills really would not matter after three years of continuous treatment. Two patients had amenorrhea after 51 and 30 cycles respectively and waited more than 10 days without pills before starting another cycle. Two other patients after 44 and 37 cycles respectively lost the pills in the Humacao flood and were at risk without protection for a week mid-cycle.

Pregnancy occurred promptly after stopping medication. Of those who discontinued norethynodrel we were able to find 241 who had been exposed to pregnancy for six months or more. Of these, 231 (96 percent) became pregnant within an average of four months, a period which may have been somewhat increased by the use of other methods of contraception. Fifty-five were pregnant within one month and 35 more within two months after discontinuing medication.

Among the 443 women who withdrew from the study, follow up showed that 169 had borne 190 babies. The mothers of 29 of these babies who could not be reached for examination reported that the babies were normal. Of the 161 examined by medical personnel 151 were found to be normal. The abnormalities of birth or anatomy described in the notes to table V show that the proportion is not greater than that to be expected for children of mothers not receiving medication.

The unpleasant side effects reported by users are grouped as follows: (See Table V).

TABLE V.—UNPLEASANT SIDE EFFECTS

Complaints	Percent of all users complaining	Percent of all users discontinuing
Reproductive system:		
Amenorrhea; breakthrough	16	2.3
Scanty menses	40	----------
Loss of libido	1	.1
Breast engorgement	1	.4
Gastrointestinal system:		
Nausea, vomiting, epigastric discomfort	43	10.9
Excessive weight gain	1	----------
Nervous system: Nervousness, headache, dizziness	35	3.3
Skin changes: Chloasma	30	.6

SIDE EFFECTS: REPRODUCTIVE SYSTEM

Decrease in Menstrual Flow with Occasional Amenorrhea. Thirty-eight patients had 50 amenorrheic cycles, or approximately 0.5 percent of the 10,400 cycles studied. This is low compared with a reported 6 percent of Tyler (10) in a study of norethindrone. These amenorrheic cycles make it important to recommence within eight days of taking the last pill whether withdrawal bleeding occurs or not. Failure to do so resulted in 5 of the 13 pregnancies which occurred due to incorrect use. It seems advisable to forewarn the patients that the menses may be less, since many of our country women have superstitions about the menses and the rumor was circulated that the periods were "weak" because the pills destroyed the blood! This we have been able to disprove to the satisfaction of our patients by demonstrating that there was no significant change in the hemoglobin level.

Breakthrough Bleeding is alarming to the uninitiated and the patients need to be forewarned. Twelve out of 121 patients who discontinued medication because of side effects dropped out because of this symptom. It was reported by 76 patients in 109 cycles for an incidence of 1 percent of the 10,400 cycles reviewed. This is also lower than 8 percent which Tyler (10) found with norethindrone. Doubling the dose on the days of breakthrough controls the bleeding.

Libido. Eleven percent of patients questioned reported decrease in libido and 7 percent reported increase; the rest noted no change. One patient discontinued because she volunteered the information that loss of libido was affecting her marriage. The elimination of the fear of pregnancy has resulted in increased marital happiness for many couples.

Increase in Vaginal Discharge or bleeding after intercourse was noted by 5 percent of the patients who had started the medication with the finding of cervical erosion at the initial pelvic examination. However, cauterization of the cervix (after a preliminary biopsy) and appropriate treatment for trichomonal infestation when present, resulted in healing of the cervix with relief of these symptoms.

Breast Changes. One percent of all users complained of breast engorgement and 0.4 percent of all users discontinued because of this side effect. Norethynodrel in the 10 mg. and 5 mg. doses started during lactation post partum was usually followed by drying of the breasts during the first or second treatment cycle. There are not yet enough observations to report on the results with 2.5 mg. dosage.

SIDE EFFECTS: GASTRO INTESTINAL SYSTEM

Nausea, Vomiting, and Epigastric Discomfort. A certain proportion of women complained of symptoms resembling the epigastric discomfort, nausea, and occasional vomiting noted in early pregnancy. However, there seems to be no correlation with the history of hyperemesis in previous pregnancies. Usually these symptoms do not persist beyond the first or second cycle. If they do, there may be a resultant loss of appetite and weight. Forty-three percent of all users in our series have complained of these symptoms at one time or another; 10.9 percent of all users withdrew because of the persistance or severity of these side effects.

Weight Change was noted by 36 percent of users: 20 percent reported gain and 16 percent loss. However, the symptom was not sufficient to lead anyone to discontinue for this reason alone. Four patients out of 838 have noted weight gain to the extent that they have requested some regime to reduce. Many patients have noted improved appetite after the initial month or two. Puerto Rican women in general prefer to be fatter than their sisters in the North.

SIDE EFFECTS: NERVOUS SYSTEM—SKIN

Headaches, Dizziness and Nervousness. Thirty-five percent of all users have complained of these symptoms Three and three-tenths percent discontinued norethynodrel for these side effects. Often the menstrual and premenstrual headache may be relieved by diuretics.

Skin Changes. Chloasma or increase in skin pigmentation of the face is a characteristic finding in pregnancy among many Puerto Rican women. Five of our patients discontinued the medication for this reason (0.6 percent of users) and 9 others who are still active users have noted marked changes. About one-third of the women have remarked on some pigmentation. Acne has not been observed in our patients.

DISCUSSION

At the beginning of our study, we were as uncertain of the outcome as our patients. We could not answer with assurance their questions as to whether the "pill" would give 100 percent protection or might result in permanent sterility or whether children born subsequently would be affected adversely. There were undoubtedly several reasons for the higher incidence of unpleasant side effects in the earlier cases. In the first place, we were asking leading questions to try to elicit all possible reactions. Secondly, we were using a higher dosage of steroid than was subsequently found to be necessary. In the second year of our study, there was much adverse press and television publicity related to any type of family planning procedure.. However, the fact that a year and a half later this became an issue in the political campaign seemed to have little effect since by that time our patients themselves were our most enthusiastic supporters. Now almost everyone who comes for family planning advice comes asking for the pills. The pill is especially acceptable because of its ease of use. This appeals to poor families who live in crowded conditions with absence of sanitary facilities. Of our 838 women of all economic and educational levels, it was necessary to advise change of method in only 6 instances because the patient could not follow instructions.

SUMMARY

Norethynodrel, with a seventieth to a twenty-fifth of its weight of ethynyl estradiol-3-methyl ether, was given in 20 daily doses, from the fifth to the twenty-fourth day of each menstrual cycle, to 838 women of proven fertility. Doses of 10 mg. were later reduced to 5 mg, and subsequently to 2.5 mg. During medication periods of 1 to 54 months and a total of 15,150 cycles in 1,165 woman years of experience, there were no pregnancies among those who carried out the instructions. Thirteen pregnancies were due to incorrect use.

Unpleasant side effects—headaches, nausea, epigastric discomfort, scanty menstruation, etc.—were reported by 43 percent of all users. These usually diminished after the early months. Side effects were named among the reasons for discontinuance by 139, and as the sole reason by 121 women. Reasons connected with the medication led to its discontinuance by 147, one for each 8 woman years of use.

Of the 241 women followed up who remained at risk of pregnancy, 231 became pregnant within an average of 4 months. One hundred and ninety babies have been born to 169 women after discontinuing norethynodrel. Of the 161 babies examined 10 showed abnormalities of birth or anatomy, a proportion not greater than that to be expected in children of mothers not receiving medication.

No evidence of damage from prolonged use of the compound has been detected. Norethynodrel provides an effective, acceptable, and reversible method of contraception.

ACKNOWLEDGEMENT

Acknowledgement is made to the valuable assistance of our social workers, Noemi Rodriguez de Diaz and Elizabeth MacDonald, and to Mrs. Paquila Torres, R.N.

REFERENCES

1. Cook, H. H.; Gamble, C. J., and Satterthwaite, A. P.: Oral contraception by norethynodrel, a three year field study, Am. J. Obst. 82:437–445, Aug., 1961.
2. Garcia, C. R.; Pincus, G., and Rock, J.: Effects of three 19-nor steroids on human ovulation and menstruation, Am. J. Ob. 75:82–97, Jan., 1958.
3. Morris, J. A.; Physiologic control of conception with norethynodrel, clinical experience, Am. J. Obst. 82:428–436, Aug., 1961.
4. Pincus, G., et al: Fertility control with oral medication, Am. J. Obst. 75: 1,333–1,346, June, 1958.
5. Pincus, G., et al: Effectiveness of an oral contraceptive, effects of a progestin-estrogen combination upon fertility, menstrual phenomona, and health, Science 130:81–83, July 10, 1959.
6. Rice-Wray, E.: Proceedings of Symposium on 19-nor Progestational Steroids, Chicago, G. D. Searle and Co., 1957.
7. Rock, J.; Garcia, C. R., and Pincus, G.: Use of some progestational 19-nor steroids in gynecology, Am. J. Obst. 79:758–767, April, 1960.
8. Tietze, C.: The cilinical effectiveness of contraceptive methods, Am. J. Obst. 78:650–656, Sept., 1959.
9. Tietze, C.: Pai, O.; Taylor, C., and Gamble, C. J.: A family planning service in rural Puerto Rico, Am. J. Obst. 81:174–182, Jan., 1961.
10. Tyler, E. T.: Oral Contraception, J.A.M.A. 175:225–226, Jan. 21, 1961.
11. Tyler, E. T., et al.: An oral contraceptive, a four year study of norethindrone, Obstet. Gynec. 18:363–367, Sept., 1961.

(Whereupon, at 3:10 p.m., the committee adjourned, to reconvene at 9:30 a.m., on Wednesday, January 21, 1970, in room 2221.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

WEDNESDAY, JANUARY 21, 1970

U.S. SENATE,
SUBCOMMITTEE ON MONOPOLY,
OF THE SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 9:40 a.m., in room 2221, New Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson, McIntyre, and Dole.

Also present: Benjamin Gordon, staff economist; Elaine C. Dye, clerical assistant; and James P. Duffy III, minority counsel.

Senator NELSON. Our first witness this morning is Dr. Clark of the University of Kentucky Medical Center, a distinguished neurologist.

Dr. Clark, we are very pleased to have you here before the committee this morning. If you could either extemporaneously or in writing submit a brief biographical background for the hearing record, that would be helpful.

STATEMENT OF DR. DAVID B. CLARK, PROFESSOR OF NEUROLOGY, UNIVERSITY OF KENTUCKY MEDICAL CENTER, LEXINGTON, KY.

Dr. CLARK. I think that can be a rather brief statement, Senator Nelson.

I am now in my later fifties. I was trained in medicine and neurology at the University of Chicago, at Johns Hopkins, and at the National Hospital in Queen Square in London; I was for 18 years an attending neurologist at Johns Hopkins, and for the last 4 years, I have been Professor of Neurology at the University of Kentucky Medical School.

I want it to be perfectly clear that I am a neurologist. I am not an internist, an expert on blood-clotting, an obstetrician, an indocrinologist, a statistician, or an epidemiologist. I deal exclusively with disorders in the nervous system.

The second point I would like to make is with regard to the drugs under discussion; as I am sure you are all aware, the oral contraceptives, commonly referred to as The Pill, are, for all practical purposes, a combination of a progestogen and an estrogen, originally given together, in recent years given, on occasion, sequentially. Most of the material I shall discuss which is all human material, derives from the period in which the drugs were given together.

These are potent drugs. Any experienced physician realizes that any drug strong enough to have a desirable therapeutic effect will be found ultimately under the right combinations of circumstances to have undesirable effects; these may be serious or, in extreme situations, even fatal. This is a hazard of all drug therapy.

One of the effects of these drugs given as contraceptives is to simulate in some part, at least, the earlier portion of a pregnancy. The simulation is not exact. There are obviously a great many differences, but in several biological respects, the woman who is on the pill might be regarded as pregnant, though the state lasts only a month and no products of conception are present.

Pregnancy itself is not a completely benign state. In the middle 1960's, the estimated maternal mortality due to the complications of pregnancy was 2.4 per 10,000, or 24 per 100,000 for whites under optimal conditions; it was 9.7 for nonwhites under frequently less than optimal conditions.

So it seems fair to assume it possible, at least, that the degree to which the biological condition of the woman who is taking the pill resembles pregnancy would also indicate the degree to which she would be exposed to the inherent risks of pregnancy.

Of course, there is one great difference. That is the very short duration of each cycle on the pill. If one indulges in a little simple arithmetic: The duration of pregnancy is statutorily 280 days; biologically, it is 266. But accepting the statutory 280 days and adding an anovulatory postpartum period of 30 days, a natural pregnancy exposes a woman to its hazards for around 310 days. If this same woman were on the pill, she would have at least 10 or 11 cycles in that time.

So if natural pregnancy and the state induced by oral contraceptives were identical, and I hasten to assure that we have no reason to assume that they are identical, then the woman on the pill has 10 times as many chances of developing a pregnancy-associated complication as the woman who had been naturally pregnant in this period of time.

I want to emphasize this is not numerically exact, and not medically proven at all. I mention it only to point out that there is reason to suspect that some of the natural hazards of pregnancy might occur in the patient taking oral contraceptives, and there is reason to suspect that they might seem to occur more frequently, since the state induced by the pill is much shorter and more frequently repeated than is a natural pregnancy.

Natural pregnancy has been recognized for decades to be attended occasionally by neurological complications. Migrainous headache very often gets a great deal worse during a pregnancy; occasionally it remains unchanged, and rarely improves. Thromboses of arteries in several parts of the body, including arteries of the brain, and thromboses of the large intracranial veins have been recognized as complications of the pregnant state decades before the pill was available. Some very reliable authorities are convinced that intracranial aneurysms, congenital dilatation of arteries at the base of the brain, are more liable to rupture during late pregnancy especially, than at other times, and there is a clear and inescapable association between pregnancy and aneurysms of arteries of the upper abdomen, which may rupture, with serious or fatal consequences.

Senator NELSON. May I interrupt for a moment?

Dr. CLARK. Yes.

Senator NELSON. On page two, when you referred to the fact that the "woman on the pill would have 10 times as many chances of developing a pregnancy-associated complication as would the woman naturally pregnant," would I be correct in saying that on the other hand, the woman, who is naturally pregnant during the course of the development of the fetus over this 9-month period, is also exposed to some of the risks that the woman on the pill is not exposed to?

Dr. CLARK. Yes, indeed, sir. This point is introduced only to indicate, Senator Nelson, that one has reason to suspect that such complications could have occurred. These things did not really appear entirely de novo. Experienced clinicians were aware of neurological and vascular complications of pregnancy, and we had to take into account that by the use of the pill, we were simulating certain parts, at least, of a natural pregnancy, that there would be certain inherent risks. The exact extent of similarity between the two conditions simply cannot be stated at the present time.

All of the neurological complications of pregnancy, the serious ones at least, with which we are concerned are rare. Only the consultant, which in the case of the nervous system, is usually the neurologist, ophthalmologist, or neurosurgeon, is apt to see any number of them, and even he does not see very many. It has been thought for a great many years that spontaneous cerebral vascular accidents are quite rare in healthy, nonpregnant women, especially younger ones; it is not surprising that the question of a relationship between the taking of oral contraceptives and strokes should have been suggested at first largely by neurologists, who would naturally tend to see a greater concentration of these problems than the general physician or obstetrician.

The first suggestive case report appeared in 1962, published by Lorentz. In the ensuing 8 years, rather better than 100 cases have been reported in the world medical literature in varying detail. One gets the impression that there are probably a great many more cases, but this is only an impression.

I should point out here that it is most unfortunate that we have no adequate and reliable reporting system to detect the existence of such cases. Over the ensuing years, an often very bitter controversy has developed over the relation between the strokes and the taking of the pill.

The reasons for this difference of opinion are quite simple. In the first place, the earlier cases were observed as sporadic events. Their numbers were very small. The physicians, who were usually neurologists or ophthalmologists, who became interested in them, had no way of knowing how many women were taking such drugs.

There was, as I have indicated, and there still is, no reliable and continuing system of reporting. There was, therefore, no way to know the total number of cases or to relate this number reliably to the number of patients who were at risk.

Further, it was rapidly found, which was embarrassing, I think, to all of us, that we did not have a really accurate idea of the incidence of spontaneous cerebral vascular accidents, spontaneous strokes, in young,

healthy, nonpregnant women. We did have some comparable information comparing incidence in women with that in men.

One well-known paper by Johnson and Walker found a preponderance of males over females of about four to one in the below-40 age group. Another, by Gurdjian, found only seven of both sexes below that age, in a series of 258 cases.

This sort of evidence tells us only something of comparable frequency between males and females and nothing of the actual incidence of spontaneous strokes in young, healthy women. So, knowning neither the expected incidence of such accidents in healthy women not on the drugs nor the actual number of people in a given population who were on the drugs, and being in doubt as to the accuracy of detection, diagnosis and reporting of cases of women who were on the drug, it was impossible to interpret the earlier reports as anything more than a cause for concern.

We were dealing, and I should like to point out that in my opinion, we still are dealing with a sort of fraction. In this fraction, we know with certainty neither the numerator nor the denominator.

Between 1965 and 1968, there was a long series of reports published by investigators who attempted to meet these difficulties. These were of two general classes. Some were studies from what were labeled stroke centers, to which patients with strokes were referred in considerable numbers. Taking this clinical material, it was possible for the investigators to compare the number of cases in young women which had occurred before the time when oral contraceptives were available with the number that occurred after these drugs were available.

Other studies were studies of strokes occurring in the population of large teaching hospitals, again using the numbers of cases and the incidences before and after the pill came to use. In both of these approaches, and especially in the latter, the absolute number of cases was very small. In both, it was impossible to relate the strokes to the relatively small population of women who were known to be taking the drugs.

These reports brought out two things. First of all, they brought out the quite interesting point that in actual fact, strokes in young, healthy women are quite possibly more common than we had realized. They were hampered, of course, by being drawn from centers for the study of such disorders. Their caseload would normally increase with time, and it still could not be easily and accurately determined with relation to the population base.

Their results are conflicting. I cite two: one is a series of 50 cases of proven cerebral vascular accidents in young women relating to the period before and after the availability of the oral contraceptive agents. This study derives from the patients in the Midlands of England. As you can see, there seems to be a clear increase in the number of cases reported after 1963, which was about the time when oral contraceptives began to be used in sizable number in Britain. This series, reported by Bickerstaff, notes that of the 25 patients seen in the center from 1964 to 1966, 18 were taking oral contraceptive drugs.

Interestingly enough, an almost identical population group reported by Jennet, from Glasgow—a very similar sort of population—is reported in the right-hand column. Jennet was impressed by the im-

portance of pregnancy as related to the occasion of these strokes in young women. He felt that there was absolutely no increase in the number of strokes after the oral contraceptive drugs became available, and indeed, he pointed out that in his 1961–65 group, 24 of the women had never taken the drugs, one had discontinued them three months before her accident occurred, and the last was not available to give information.

Similar conflicting reports on strokes were made by various American centers; among others, two fairly well-known ones were those reported from Duke University and the Mayo Clinic.

In the last 2 years, two carefully controlled studies have been reported. One was really a group of studies performed in Britain by Inman and Vessey, and later by Vessey and Doll, and one was reported in the last several weeks by Sartwell and his associates from Johns Hopkins. These, again, were retrospective studies. I am sure you are all aware by now, with complications of an apparently quite low incidence, such as strokes or other thromboembolic accidents, a prospective study in which one selects a large group of women who are going on the drug and follows their career for the ensuing months or years is extremely difficult an extremely costly because of the large number of women who must be studied and the length of time which they must be studied. Most authorities have elected, rather, to go to the accident, to select the patients who have already developed an accident and then go back and try to relate this to their drug habits and other social, medical, and economic practices.

The studies from England, and from the northeastern portion of this country reported by Sartwell, were retrospective studies, in which cases of thrombophlebitis, pulmonary embolism, stroke, and, in the British series, coronary occlusion, were identified through hospital and physicians' records. These were analyzed for the presence or absence of possible contributing causes such as previous trauma, high blood pressure, infections, and obesity, and suitable matched controls from the same patient populations were selected and similarly analyzed.

Following this, cases and controls were then interviwed personally.

The results of these two studies were very similar. Both indicate an increased risk of thromboembolism and stroke in the users of oral contraceptives. The British study has suggested that the overall increased risk for all forms of thromboembolic disease and stroke might be as high as eight or nine times the expected rate. The American study suggested that the increased hazard was of the order of four and a half times the risk to nonusers of the drug.

Though the risk seems to be real, the absolute numbers remain small. The British figures, which are rather the higher of the two, do not suggest a range of death rate from vascular accident which might be attributable to The Pill—all forms of thromboembolic disease, including stroke as well—greater than 1.5 to about 3.5 per 100,000. The 1.5 would relate to women of the younger age groups, the 3.5 to older age groups.

Similar rates in this study for nonusers were about two-tenths to five-tenths per 100,000. Now, since thrombosis of deep veins in the legs and pulmonary embolism are much more common than stroke in the

groups studied, women in the child-bearing years, whether they take oral contraceptives or not, it is obvious that the death rate from stroke which could be attributed to The Pill must be quite small. These figures of increased hazard ranging from an expected one of two-tenths to five-tenths per 100,000, being increased to 1.5 to perhaps 3.5 per 100,000—apply to all forms of vascular accident and not to strokes alone.

In the absence of clearer epidemiologic data, I think it is well to look more closely at the strokes themselves, the ones we might consider as being possibly related to the taking of The Pill. If these are different from any other form of recognized stroke, this would strengthen the conclusion that they might be related to the taking of the drugs. There are some suggestions that the strokes which have occurred in women taking the pill may be different in thir manifestations and their method of development from more commonly occurring strokes.

The rest of this information is derived from an analysis of my own 59 cases. Some of these are my own personal cases. Some of them have been referenced to me by other physicians, and some of them have been taken from the published literature. One cannot use all the published cases in the literature, because in many, it is impossible to find anything like as detailed information that is necessary for adequate analysis.

In looking at this group of strokes, it seems their time of onset is often prolonged, for days, and even weeks. In a considerable portion of the cases, the onset was marked by premonitory migrainous headache. The patient may have attacks of double vision, they may have transitory weakness in various parts of the body, which recovers for a time; they often report giddiness and fainting attacks, and this finally develops into a full-blown stroke.

This occurs in at least a quarter of these strokes and does not seem to be related to the presence of arteriosclerosis. We are not unfamiliar with the occasion of premonitory symptoms of the stroke in the patient who is older and has severe arteriosclerosis. In these cases, such are believed to be due to the breaking off of emboli on plaques of arteriosclerosis. These break off and pass up to the brain before a full-blown stroke develops. In the women under question, there is little significant evidence for arteriosclerosis. So I think it is possible that such premonitory symptoms for days or weeks before the full-blown stroke develops may be a reason for assuming a seeming association with the pill.

Secondly, in a very few autopsied cases, and very few autopsies are reported, there is microscopic evidence that a slow process of occlusion of arteries and then healing may have been going on in several parts of the brain for sometime before a major artery is involved.

These changes, in at least a few of the autopsied cases, do not strictly resemble the sort of change one is accustomed to see in the commonly occurring strokes with which we are all familiar.

Thirdly, the arteries that pass to the base of the brain, the vertebral and basilar arteries, seem to be involved more often than one would expect, especially in a group of patients who, in the main, are not significantly hypertensive and do not have significant arteriosclerosis.

Fourthly, of course, the age incidence is unusual. In this group, in my own analysis, the age incidence is as you see. In the 20 to 24 group, 13; in the 25 to 29 group, 14; in the 30 to 34 group, 16; 35 to 39, 1; and then just a handful above 40. This certainly reflects the child-bearing years, but it does not show, to my mind, the steady increase with increasing age one would expect if the strokes were simply a consequence of the hypertension, arteriosclerosis, and so on one would expect in advancing years.

I should point out in this respect, this analysis in a small number of cases does not agree with the British analysis, which found a much higher incidence in the older women. It does, however, agree with the Baltimore study.

Fifth, although the mortality of the patients who had stroke is fairly high, eight of 59, or approximately 15 percent in this group, the survivors seem to make surprisingly good recoveries. Of the 51 in this group, about two-thirds made, as far as we could discover, complete recoveries from their strokes.

Another point of interest that is, I think, deserving of mention is that although stroke involving the cerebral blood vessels and thromboembolism involving the large veins of other parts of the body are the subjects under discussion, another form of arterial disease, coronary artery disease, which certainly is very commonly seen in association with stroke in older people, does not in any of the available studies clearly related or in any way associated with the taking of the birth control drugs.

These differences suggest a search for a different mechanism for the strokes and thromboembolic effects of the pill. I shall not go into this in detail. It is not in my area of competence. You have other witnesses this morning who can speak with much greater significance to this point. It is, however, worth pointing out that this difference may be found in the change in the constituents and the clotting mechanisms of the blood.

It is known that synthetic steroids have a rather dramatic effect on various constituents in the blood and the various factors that are involved in the formation of a clot. So that mechanisms, at least for alterations in the normal clotting behavior, are certainly present.

There is some reason also to believe that there may be changes in the vascular wall itself. It is known that estrogens have an effect on the caliber of veins. In some of the stroke victims who have been studied, there is a pecular beaded appearance to the walls of the arteries which were apparently involved—not occulsion, but irregularity of outline that suggests there may be edema or other changes in the outer wall of the artery concerned.

Lastly, and rather parenthetically, I should point out to you that a number of other questions are under consideration at the moment. One is the possible significance of the estrogen fraction in the birth control pills. The other is the possible relationship of the development in these thromboses to certain blood types. Some authorities believe that type O patients are singularly immune to such attacks.

I think we might summarize this as follows: the steroid drugs used produce in their recipients a state which, to some degree, resembles pregnancy. Pregnancy is itself known to be accompanied by an in-

creased incidence of disorders of blood vessels and blood clotting. There is evidence that blood clotting mechanisms, constitutents of the blood, and possibly blood vessel walls are or can be altered by contraceptive steroids.

There is, further, the conviction on the part of many cautious and experienced clinicians that strokes are now more frequently seen in young women taking the pill. I think one can summarize as follows: First, there does seem to be a relationship between the taking of currently used oral contraceptives—the pill—and the evolution of a strokelike syndrome or a frank stroke.

Second, it is regrettable that no effective system of reporting possible complications is in operation to give at least a fairly accurate idea of the number of cases occurring in a large population in a prospective rather than retrospective sense.

Third, the strokes themselves usually involve arteries rather than veins, though both may be affected. They do not seem to require preexisting disease of the arteries, such as arteriosclerosis, to develop, though such may contribute, especially in the older women.

Fourth, the most acceptable evidence at present suggests that the strokes related to taking the pill are brought about either by changes in the chemical and enzymatic composition of the blood, or by intracellular changes in the vessel walls, or possibly by both.

Fifth, since the actual incidence of such strokes is not known, mortality cannot be estimated accurately. A rough estimate based on pubblications suggests about 15 percent.

Sixth, as far as can be estimated at present, the prognosis for a good or virtually complete recovery in the survivors is at least 50 percent.

Seventh, there is reason to believe that women with hypertension or with a previous history of occlusive disorders of blood vessels are more at risk. Certainly, any woman taking the drugs who begins to have migrainous headaches, in whom previously present migraine is worsened or who experiences any disturbance of speech, vision, motor coordination, or sensation, should stop the drugs at once.

Thank you, sir.

(The complete prepared statement and supplemental information submitted by Dr. Clark follows:)

STATEMENT OF DR. DAVID B. CLARK, PROFESSOR OF NEUROLOGY, UNIVERSITY OF KENTUCKY MEDICAL CENTER, LEXINGTON, KY.

I should like at outset to make a few points clear. *First*, with regard to myself and my own qualifications, I am a neurologist. My area of clinical competence lies in the disorders of the nervous system. I am neither an obstetrician, an endoctrinologist, an internist, an epidemiologist, nor a statistician. I shall therefore restrict my comments to the question of neurological disorders possibly related to the taking of oral contraceptive agents, and specifically to strokes. My material is derived from my own cases, those referred to me by other physicians, and from the now extensive literature on the question.

Second, with regard to the drugs under discussion. The oral contraceptive agents are for practical purposes, combinations of a progestogen and an estrogen, originally given together, now in some instances given sequentially; sequential administration is a relatively recent development, and most of the material I shall discuss derives from those cases in which estrogen and progestogen were given together.

These are potent drugs. It is an axiom of therapeutics, which every physician must learn sooner or later, that any drug potent enough to have desirable thera-

peutic effects will be found, sooner or later, under the right combination of circumstances, to have undesirable, serious or fatal effects as well. To a degree at least, this is a hazard of all drug therapy.

One of the effects of oral contraceptives is to simulate, to some extent, a pregnancy or at least the earlier portion of a pregnancy. There are obviously many points of difference, but in several biological respects the woman on "The Pill" is pregnant, though the state lasts only a month, and no products of conception are present. Pregnancy is itself not a completely benign state; in 1965 the maternal mortality in this country was 2.4 per 10,000 for whites under optimal conditions of care, and 9.7 for non-whites under less than optimal conditions. It seems fair to assume then, that to the degree that the biological condition of the woman taking "The Pill" resembles pregnancy, she must be expected also to be exposed to the inherent medical hazards of pregnancy.

One great difference, of course, is the much shorter duration of each cycle on the pill.If one accepts the duration of pregnancy as 280 days, plus an anovulatory post partum period of about 30 days, one natural pregnancy exposes a women to its medical hazards for 310 days. If on "The Pill" she will have had at least 10 pill cycles in that time. If natural pregnancy and the state induced by oral contraceptives were identical in risk, (and we have no reason to assume that they are identical) the woman on "The Pill" would have had ten times as many chances of developing a pregnancy-associated complication as would the woman naturally pregnant.

I emphasize—this is in no sense numerically exact or even medically proven. I mention it only to point out that there is reason to suspect that some of the natural hazards of pregnancy might occur in patients taking oral contraceptive agents; there is reason to suspect that they might seem to occur more frequently, since the state induced by the pill is so much shorter and more frequently repeated than is natural pregnancy.

Natural pregnancy has been recognized for decades to be attended occasionally by neurological complications. Migrainous headache often worsens, rarely improves, during pregnancy. Thromboses of arteries, or of the large intracranial veins were recognized as complications of the pregnant state decades before The Pill was available. Some authorities believe that intracranial aneurysms—congenital dilatations of arteries of the brain—are more liable to rupture during late pregnancy than at other times, and there is a clear and inescapable association between pregnancy and aneurysm of arteries of the upper abdomen.

All of these as complications of pregnancy are rare. Only the consultant—in the case of the nervous system, the neurologist—is apt to see any number of them and even he does not see many. Since spontaneous cerebral vascular accidents have for years been thought to be very rare in healthy, non-pregnant women, especially younger ones, it is not surprising that the question of a relationship between oral contraceptives and strokes should have been suggested at first largely by neurologists, who would naturally tend to see a concentration of such problems.

The first suggestive case report appeared in 1962. In the ensuing eight years, rather better than 100 cases have been reported in the world medical literature in varying detail, in which an association between the taking of oral contraceptives and the occurrence of a stroke has been suspected. In this time, an often bitter controversy developed over the relationship, if any, of the strokes to the taking of the drugs.

The reasons for this difference of opinion are simple. In the first place, the earlier cases were necessarily observed as sporadic events; their numbers were small. The physicians, usually neurologists or ophthalmologists, who became interested in them had no way of knowing how many women were taking such drugs. There was and is no reliable and continuing system of reporting, and there was therefore no way to know the total number of cases, or to relate this number reliably to the number of patients at risk.

Further, it was rapidly found that physicians had no really accurate idea of the incidence of spontaneous cerebral vascular accidents in young, healthy, non-pregnant women. Available data suggested a very low rate; Johnson and Walker, for example, found a preponderance of males over females of 4:1 in the below forty age group, and Gurdjian only seven of both sexes below that age, in a series of 258 cases. This sort of evidence, however, tells us only something of comparable frequencies between males and females, and nothing of actual incidence of spontaneous strokes in young healthy women. Knowing neither the expected in-

cidence of such accidents in healthy women not on the drugs, nor the actual number of women in a given population on drugs, and being in doubt as to the accuracy of detection, diagnosis, and reporting of cases in women on the drug, it was impossible to interpret the earlier reports as anything more than a cause for concern. We were dealing with a fraction, of which we knew with certainty neither numerator nor denominator.

Between 1965 and 1968 several investigators published reports in which they attempted to meet these difficulties. These reports were of two general kinds. Some were studies from stroke centers, to which patients with stroke were referred in considerable numbers. With such clinical material, it was possible to compare numbers of cases in young women occurring before and after the time when oral contraceptives became available. Others were studies of strokes occurring in the population of large teaching hospitals, again using numbers of cases and incidences before and after The Pill came into use. In both of these approaches, and especially the latter, the absolute number of cases were very small, and in both it was impossible to relate strokes to a well-defined population of women taking the drugs.

These reports brought out the interesting point that strokes in young healthy women are quite possibly more common than was realized, but they were hampered by being drawn of necessity, from centers for study of such disorders, whose case load would normally increase with time, and by the fact that the case load could not easily be related to a population base. Their results are conflicting as in the following example:

STROKES IN WOMEN (15 TO 45 YEARS OF AGE)

	Bickerstaff—50 cases			Jennet—65 cases		
	No O.C.	O.C.	T	Pregnant	Nonpregnant	T
1954	2		2			
1955	1		1			
1956	2		2	0	4	4
1957	4		4	3	2	5
1958	3		3	5	2	7
1959	2		2	2	3	5
1960	1		1	2	5	7
1961	2		2	1	1	2
1962	4		4	4	4	8
1963	4		4	2	5	7
1964	2	4	6	0	6	6
1965	2	4	6	4	10	14
1966	3	10	13			
Total	32	18	50	23	42	65

Bickerstaff, drawing his patients from the Midlands, seems to have seen a clear increase in patients in the 1960's, and notes that of the 25 patients seen 1964–66, 18 were on oral contraceptives. Jennet, in Glasgow, felt there had been no increase in such accidents, and noted that of the twenty-six non-pregnant women in his 1961–65 group, 24 had never taken such drugs, one had discontinued them three months before her accident, and the last gave no information. Similarly conflicting reports were made by various American centers, among others those reported from Duke University and the Mayo Clinic.

In the last two years two carefully controlled studies were reported, one from England by Inman, Vessey, and Doll, and one from the United States by Sartwell and his associates. These again were retrospective studies in which cases of thrombophlebitis, pulmonary embolism, stroke, and in the British series, coronary occlusion were identified through hospital and physicians records. These were analyzed for presence or absence of possible contributing causes such as trauma hypertension, obesity, infections, etc., and suitable matched controls were selected and similarly analyzed. Cases and controls were then interviewed personally.

The results of these two studies were similar. Both indicate an increased risk of thromboembolism and stroke in the users of oral contraceptives. The British study suggested that the increased risk may be as high as eight or nine times, the American that it was of the order of four and one-half times that of the risk to non-users.

Though the risk is evidently greater, the absolute numbers remain small. The British figures, rather the higher of the two, do not suggest a range of death

rate from all forms of thromboembolism including stroke, greater than 1.5 :100,000 in young women users to 3.9 :100,000 in older users. Similar rates for non users are 0.2 to 0.5 :100,000. Since deep vein thrombophlebitis and pulmonary embolism are much more common than stroke, in women in the child-bearing years, whether they take oral contraceptives or not, it is obvious that the death rate from stroke which could be attributed to the use of "The Pill" is quite small.

In the absence of clearer epidemiological evidence, it is worthwhile to look more closely at the strokes themselves. There are some suggestions that the strokes occurring in women taking "The Pill" may be different in their form and in their method of development from more common forms.

First, their onset is often prolonged, for days or even weeks, marked by premonitory migrainous headache, attacks of double vision, transitory weakness which recovers for a time, giddiness and syncopal attacks, which eventually develop into a full-blown stroke. This sort of onset is fairly common in older patients, where it is apparent due to the breaking off of small emboli from plaques of arteriosclerosis. The young pill users, however, often do not have arteriosclerosis at all.

Second, in a few autopsied cases, there is microscopic evidence that a slow process of thrombosis and then healing has been going on in several parts of the brain for some time before a major vessel was involved.

Third, the vertebral and basilar arteries, at the base of the brain, seem to be involved more often than one would expect, especially in the quite young women who have never had any hypertension and have no arteriosclerosis at all.

Fourth, the age incidence is of course unusual. In 59 cases now being analyzed, some my own, many from the literature, this was as follows :

20—24 :	13
25—29 :	14
30—34 :	16
35—39 :	11
40—44 :	3
45+ :	2

This certainly reflects the childbearing years, but it does not show the steady increase one would expect if the strokes were simply due to the increasing incidence of hypertension, arteriosclerosis, and other medical diseases which could lead to stroke. It may simply reflect the incidence of use of "The Pill" in various age groups—though older child bearing women are often quite anxious to avoid further pregnancy.

Fifth, although mortality is fairly high, eight of fifty-nine, or 15.7% in this group, the survivors seem in most cases to make surprisingly good recoveries; about two thirds of the fifty-one in this group made good to complete recoveries.

Sixth, although coronary artery disease is a common concomitant of strokes as known in older people, there is as yet no good evidence that there is a concomitant increase in coronary disease in women on the pill.

These differences suggest a search for a different mechanism for the strokes and thromboembolic effects of "The Pill". This may be found in the changes in constituents and clotting mechanisms in the blood. It is known that synthetic steroids alter the lipoprotein pattern of blood plasma toward the male one, increasing the low density lipoproteins, triglycerides, cholesterol, and high density lipoproteins. They may cause an increase in alpha and beta globulins, and C—reactive protein, while decreasing serum chloesterinase and albumin. They increase serum iron, iron-binding capacity, prothrombin time, fibrinogen, and profoundly effect fibrinolytic activity and the Factor VII–X complex of the clotting system. Mechanism, at least, for alterations in normal clotting behavior are certainly present.

The steroid drugs used produce in their recipients a state which to some degree resembles pregnancy, a condition known to be accompanied by an increased incidence of disorders of blood vessels and blood clotting. There is evidence that blood clotting mechanisms, constituents of the blood, and carbohydrate metabolism are significantly altered by contraceptive steroids. There is further, the conviction on the part of many cautious and experienced clinicians that such cerebral accidents are now more frequently seen. It seems safe to conclude the following :

(1) There does seem to be a relationship between the taking of currently used oral contraceptives—"The Pill"—and the evolution of a stroke like syndrome or a frank stroke.

(2) It is regrettable that no effective system of reporting such possible complications is in operation to give at least a fairly accurate idea of the number of cases occurring over a large population, in a prospective rather than retrospective sense.

The strokes themselves usually involve arteries rather than veins, though both may be affected. They do not seem to require pre-existing disease of the arteries, such as arteriosclerosis, to develop, though such may contribute, especially in the older women.

(4) The most acceptable evidence at present suggests that the strokes related to taking "The Pill" are brought about either by changes in the chemical and enzymatic composition of the blood, or by intracellular changes in the vessel walls, or possibly by both.

(5) Since the actual incidence of such strokes is not known, mortality cannot be estimated accurately. A rough estimate based on published cases suggests about 15%.

(6) As far as can be estimated at present, the prognosis for a good or virtually complete recovery in the survivors of a stroke is about fifty percent or slightly better.

REFERENCES

1. Ask-Upmark, E., *Thromboembolism and Oral Contraceptives: Post or Propter?* Acta, Med. Scand. 179:463–73, April 1966.
2. Bickerstaff, E. R. and Holmes, J. M., *Cerebral Arterial Insufficiency and Oral Contraceptives.* Brit. Med. J. 1:726–729, March 1967.
3. Bradford, D. E., *Cerebral Thrombosis and Oral Contraceptives.* Brit. Med. J. 1:679–688, March 1967.
4. Cole, M., *Strokes in Young Women Using Oral Contraceptives.* Arch. Intern. Med. 120:551–555, Nov. 1967.
5. Drill, V. A. and Calhoun, D. W., *Oral Contraceptives and Thromboembolic Disease.* JAMA 206:77–84, Sept. 1968.
6. Ehtishamuddin, M., *Vertebral Artery Thrombosis and Oral Contraceptives.* Brit. Med. J. 2:921–922, April 1965.
7. Filippa, G., Regli, F., Noseda, G., *Kausalzusmmengange Zwischen Einnahme Kontrazeptiva und Neurologischen Komplikationen?* Munchener Med. Wsch., 109:691–698, March 1967.
8. Gurdjian, E. S., Hardy, W. G. and Lindner, D. W., *The Surgical Considerations of 258 Patients with Carotid Artery Occlusion.* Surgery, Gynec. Obstet. 110:327–338, March 1960.
9. Haller, J., *Thrombose und Hormonbehandling,* Deutsche Medizinische Wochenschrift, 90:2124–2125, November 1965.
10. Humphrey, J. G. and Newton, T. H., *Internal Carotid Artery Occlusion in Young Adults,* Brain, 83: 565–578, 1960.
11. Illis, L., Kocen, R. S., McDonald, W. I., Mondkar, V. P., *Oral Contraceptives and Cerebral Arterial Occlusion.* Brit. Med. J. 2:1164–1166, Nov. 1965.
12. Inman, W. H. W. and Vessey, M. P., *Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child Bearing Age,* Brit. Med. J. 2:193–199, Apr. 1968.
13. Jennet, W. B., and Cross, J. H., *Influence of Pregnancy and Oral Contraception on the Incidence of Strokes in Women of Child Bearing Age.* Lancet, 1:1019–1023, 1967.
14. Johnson, H. and Walker, A. W., *The Angiographic Diagnosis of Spontaneous Thrombosis of the Internal and Common Carotid Arteries,* J. Neurosurgery, 8:631–659, 1951.
15. Lorentz, I. T., *Parietal Lesion and "Enovid",* Brit. Med. J., 2:1191, Nov. 1962.
16. Nevin, N. C., Elmes, P. C., Weaver, J. A., *Three Cases of Intravascular Thrombosis Occurring in Patients Receiving Oral Contraceptives.* Brit. Med. J., 1:1586–1589, June 1965.
17. Oliver, M. F., *Oral Contraceptives and Coronary Thrombosis.* Brit. Med. J., 2:301, July 1965.
18. Salmon, M. L., Winkelman, J. Z., Gay, A. J., *Neuro-Ophthalmic Sequelae in Users of Oral Contraceptives.* JAMA 206:85–91, 1968.
19. Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E., *Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study.* Am. J. Epilem. 90:365–380, 1969.
20. Scorey, J., *Oral Contraceptives and Thrombosis.* Brit. Med. J., 2:301, July 1965.

21. Shafey, S., and Scheinberg, P., *Neurological Syndromes Occurring in Patients Receiving Synthetic Steroids (Oral Contraceptives)* Neurology, 16:205–211, 1966.
22. Sheets, R. and Larsen, S., *CPC #482-Young Woman, Oral Contraceptives, Thrombosis.* J. Iowa Med. Soc., 57:824–34, Aug. 1967.
23. Somers, J., *Recurrent Stroke Associated with the Use of Synthetic Steroids,* Missouri Med., 64:717–719, 1967.
24. Stewart, Wallace, A. M., *Cerebrovascular Accidents and Oral Contraception.* Brit. Med. J., 2:1528–1529, Dec. 1964.
25. Vessey, M. P. and Doll, R., *Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease.* Brit. Med. J., 2:199–205, 1969.
26. Vessey, M. P. and Doll R., *Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report.* Brit. Med. J., 2:651–657, 1969.
27. Walsh, F., Clark, D. B., Thompson, R. S., Nicholson, D. H., *Oral Contraceptives and Neuro-Ophthalmologic Interest.* Arch. Ophthal., 74:628–640, Nov. 1965.
28. Whitty, C. W. M., Hackaday, J. M., Whitty, M. M., *The Effect of Oral Contraceptives on Migraine.* Lancet, 1:856–859, April 1966.
29. Zilkha, K. J., *Cerebrovascular Accidents and Oral Contraception.* Brit. Med. J., 2:1132–1133, Oct. 1964.

CURRICULUM VITAE

David Barrett Clark, M.D.
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Education

Ph.D., University of Chicago, 1939
M.D., University of Chicago, 1946

Appointments

Research Assistant (Instructor) Neuroanatomy, University of Chicago, 1938–1945.
Neuropathologist, Children's Memorial Hospital, Chicago, Illinois, 1942–1946.
Intern in Pediatrics, University of Chicago, January 1–June 30, 1947.
Intern in Medicine, Johns Hopkins Hospital, Baltimore, Maryland, July 1, 1947–June 30, 1948.
Assistant Resident in Neurology, Johns Hopkins Hospital, Baltimore, Maryland, July 1, 1948–June 30, 1949.
Instructor to Associate Professor, Medicine, Pediatrics, Pathology, Johns Hopkins Hospital, Baltimore, Maryland, 1949–1965.
Associate Professor, Medicine & Pediatrics, Johns Hopkins Hospital, School of Medicine, Baltimore, Maryland, 1958–1965.
Attending Neurologist & Pediatrician, Johns Hopkins Hospital, Baltimore, Maryland, 1952–1965.
Attending Neurologist, Rosewood State Training School, Baltimore, (Owings Mills) Maryland, 1954–1965.

Present Faculty and Hospital Appointments

Professor and Chairman, Department of Neurology, University of Kentucky Medical Center, 1965–
Professor of Pediatrics, University of Kentucky Medical Center, 1965–

Societies and Board Qualifications

Phi Beta Kappa, Sigma Xi, Alpha Omega Alpha.
American Board of Psychiatry & Neurology in Neurology, 1954.
American Medical Association.
Southern Medical Association.
Royal Society of Medicine.
American Academy of Neurology.
American Neuropathological Association.
American Neurological Association.
Member, various NINDB study sections, 1958–1964.
NINDB Training and Research Committee A, 1965–1969.

Lectureship

Teale Lecturer, Royal College of Physicians, 1967.

National Committees

Medical Advisory Board, Epilepsy Foundation of America, 1966—Trustee, Association of Professors of Neurology, 1967–1968.

Fellowships

William H. Wilder Fellow in Anatomy, University of Chicago.

Fulbright Lecturer in Neurology, 1950–1951, (National Hospital, Queen Square, London).

Bibliography

The Human Spinal Cord 20 Years After Total Transection, University of Chicago, Dissertation, 1940.

Various Restricted Reports, the O.S.R.D. on Chemical Warfare, 1942–45.

Oxygen Uptake of Spinal Ganglion Cells, with J. M. Tobias (Trans. American Neurological Society) 1941.

Herodopathia Atactica Polyneuritiformia, Procedures of the Royal Society of Medicine, 1951.

Clinical Pathological Conference. Abscess of Anterior Pituitary. Neurology 3:1953, pp. 858–863.

Brain Abscess Complicating Cyanotic Congenital Heart Disease, Trans. American Neurological Society, 1952 (with E. S. Clarke) pp. 73–76.

Thrombosis of the Basilar Artery with Softenings in the Cerebellum and Brain Stem, due to Manipulation of the Neck (with F. R. Ford) Bulletin-Johns Hopkins Hospital, 1956, pp. 37–42.

Incidence of Neurological Complications in Congenital Heart Disease (with H. Richard Tyler) A.M.A. Archives of Neurology & Psychiatry, January, 1957, Volume 77, pp. 17–22.

Cerebral Vascular Accidents in Congenital Heart Disease (with H. Richard Tyler) A.M.A. Archives of Neurology & Psychiatry, 77:17–23, Jan. 1957.

Loss of Consciousness and Convulsive Disorders in Patients with Congenital Heart Disease (with H. Richard Tyler) A.M.A. Archives of Neurology & Psychiatry, 79:506–510, May, 1958.

Section on Neurological Disease in Michell-Nelson's *Textbook of Pediatrics*, 1959.

Neurologic Complications in Patients with Coarctation of the Aorta, Neurology 8:712–717, 1958 (with H. R. Tyler).

Reflex Observations in Phenylketonuria (with J. H. French, R. D. Teasdall, & H. Butler) Journal of Pediatrics 58 (1):1722, January, 1961.

Correlation of Complications of Labor with Lesions in the Brains of Neonates (with G. W. Anderson) J. Neuropathology & Exp. Neuro. 20 (3):275–278, April, 1961.

Infantile Amaurotic Familial Idiocy (Tay-Sachs Disease) in the Negro Race (with J. Duke) Amer. J. Ophthal. 53 (5):800–805, Mat. 1962.

Management of Acute, Ineffective Polyneuritis. In Gellis & Kagan's *Current Pediatric Therapy*, 1963.

Diseases of the Muscles. In Nelson's *Textbook of Pediatrics*, 1963.

Oral Contraceptives and Neuro-Opthalmologic Interest (with F. B. Walsh, R. S. Thompson, D. H. Nicholson) Arch. Ophthal. Vol. 74, pp. 628–640, Nov. 1965.

The D_1 Trisomy Syndrome: Three Subjects with Unequally Advancing Development (with C. S. N. Lee, S. H. Boyer, P. Bowen, D. J. Weatherall, H. Rosenblum, J. R. Duke, C. Liboro, W. Bias & D. S. Borgaonkar) Bulletin, Johns Hopkins Hospital, 1966, pp. 374–394.

Hereditary Partial Agenesis of Corpus Callosum (with J. H. Menkes & M. Philippart) Arch. Neuro. Volume 11, pp. 198–208, August, 1964.

Brain Abscess and Congenital Heart Disease, Cl. Neurosurgery, Vol. 14, 1967.

Benign VI Nerve Palsies in Children (with D. L. Knox & F. F. Schuster) Pediatrics Volume 40, No. 4 Part I, October, 1967.

Acanthocytosis and Neurological Disorder without Betalipoproteinemia (with E. M. R. Critchley & A. Wikler) Arch. Neuro. Vol. 18, February, 1968.

Focal Pyogenic Diseases of the Brain and Spinal Cord. In Brennemann's *Practice of Pediatrics*.

Brain Abscess. In Holt & McIntosh, *Pediatrics*.

The Pathogenesis of the Syndrome of Minimal Brain Damage. Teal Lectureship, Royal College of Physicians, 1968.

Senator NELSON. Are there any neurological symptoms that you can think of that the user of the drugs should be notified about and which do not now appear in the package insert, for example, in the contraindications and side effects?

Dr. CLARK. I really could not answer that accurately, Senator Nelson. I have not reviewed those package inserts in the last year or so. I am not certain.

Senator NELSON. Have you listed here all the neurologic symptoms that would occur to you that ought to alert a user to consult a physician, or are there others?

Dr. CLARK. I should think that under section 7 on page 10, I listed the important symptomotology which should excite suspicion.

Senator NELSON. You do not think of others that would be of significance?

Dr. CLARK. No, sir.

Senator NELSON. I think all the witnesses who have testified, on questioning, have all regretted the lack of adequate reporting systems to give us sufficient data on a large statistical basis. Do you have any suggestions as to what the answer to that is?

Dr. CLARK. Well, I am afraid that my suggestions might not be very well received, Senator Nelson, because they all cost money.

Senator NELSON. Well, what would be the suggestion if you had the money?

Dr. CLARK. You see, studies of this sort require a large staff of highly trained people. It is getting pretty hard to staff an organization with such people. In my own institution, which is very generously supported by the State, I have a keen interest in this problem, but I have a department to run; I have to teach medical students, and I have to take care of epileptics, and I have to do a lot of things. Just the time of sufficiently trained people is very short.

You ask how one would do it. I should think that one should begin by forming a registry of cases, just in this small area of my own interest, the strokes. One should begin, in sizable population areas, mandatory registration of all strokes known to occur in women who are in the childbearing age group for a few years. Then we can at least identify the cases.

Moving on from that, we would run into a very expensive, although very productive study, because this has to be analyzed very carefully. I think one of the complaints that can be justifiably raised about many of these studies is that you find yourself on the horns of a sort of dilemma.

If you study your cases intensively, you can study only a very few. If you start working with a large enough group of cases or a large enough population base so that your figures become reliable, you find yourself moving farther and farther from the patients. And anyone who has been an active clinician for years knows that there is no substitute for a very close contact and a fairly close personal relationship with patients before the facts come out. They do not come out in a nice, mail-order questionnaire, or something of that sort. You just have to spend a good deal of time with these women before you really get all the information that is pertinent to the problem.

This takes many trained people and many, many hours.

Senator NELSON. Considering that this particular drug is prescribed to more than 8 million healthy people, would it not be worthwhile, in fact, necessary perhaps, for the Federal Government to outline a procedure on a rather substantial scale for finding out important information about it?

Dr. CLARK. I think that certainly someone should do this, Senator Nelson. Professor Walsh, at Hopkins, and I attempted to make a suggestion of that sort in the autumn of 1965 in a paper that we published bearing on this problem.

Senator NELSON. In 1965?

Dr. CLARK. Yes, sir. The purpose of publishing that paper and the purpose of an editorial that Professor Walsh wrote for the Archives of Ophthalmology was to call this to attention.

Senator NELSON. Would you give us the citation on that particular paper, or is it listed in your paper?

Dr. CLARK. The reference is the Archives of Ophthalmology, volume 74, pages 628–640. This appeared in November of 1965, sir.

Senator NELSON. Thank you very much, Doctor, for your testimony.

Senator Dole?

Senator DOLE. Dr. Clark, first let me apologize for being late, but I have read your statement. There is much about the pill that I do not understand. I assume there is much about it that no one understands; otherwise, we would not be having these hearings. But do I understand correctly that you have made your own studies based on your own cases?

Dr. CLARK. Not entirely, Senator. The group that I am referring to right now is still under analysis, this group of 59 patients. The first publication that I made on the subject was with Professor Walsh. At that time, we had over 30-odd cases of various sorts of vascular accidents. They were collected from friends all over the world. There was very little published material at that time.

Now, since that time, I have had a chance to study personally 21 or 22 cases where I feel there may be a relationship between the taking of the drugs and the development of a stroke. The remainder of the cases that I mentioned—it was a group of 59—are those that have been published by other authorities in very considerable detail that could be analyzed, or where I have been able to make personal contact with a man who published, because I knew him—he was a friend of mine, and I could get access to the cases.

These 59 are not all my cases.

Senator DOLE. Your studies are based on 21 cases that you have personal knowledge of?

Dr. CLARK. Yes.

Senator DOLE. Again, you were looking, I assume, for most everything, but were you looking particularly with reference to taking the pill and its relationship to possible stroke? Is that it?

Dr. CLARK. That was the point, yes.

Senator DOLE. And based on those 21 personal studies, is there any synopsis available, any summary available, of those 21 case studies that you might have?

Dr. CLARK. This is a big job, and I would rather not try to summarize this. We are still working through these cases. There are many details that one still wants to collect on them.

Senator DOLE. You have apparently done research. Are you now able to reach any strong conclusions with reference to the pill based on these 21? Or are you still in the process of more research?

Dr. CLARK. I think all of us who are interested in this problem, Senator, are in the process of a great deal more investigation. I do think, though, that the conclusions that are listed on page 9 are ones about which I feel rather strongly. I am confident that in these cases, there are strokes whose manifestations and whose apparent pathology in the surviving cases, in which it has to be revealed largerly by methods such as arteriography, and whose actual pathology in fatal cases suggests that there is a rather different mechanism at work from the ordinary sort of stroke, and that this mechanism seems to be related to changes in the blood-clotting, and possibly blood vessel walls. Since both of these are known to be affected by various fractions of the oral contraceptive agents, I believe there is reason to believe that these strokes may be related to the taking of the pill.

Senator DOLE. Are you ready at this time to kill the pill?

Dr. CLARK. Senator, I am not here to kill or to revivify anything. As I told you, I am a neurologist. I am interested in these strokes. I can conceive it within my purview to try to find out as much about them as I can. The question of using various means of controlling the population is a much larger one that would have to be dealt with by experts in that field and not by me.

Senator DOLE. My point is that there has been a strong ratio of anti-pill witnesses, maybe not by design but by fact, about seven to one. I assume that there will be a balanced hearing. If not, we should try to balance it with other witnesses, because I think there are probably two sides. There must be certain advantages to the pill other than avoiding pregnancy.

I think we probably have terrified a number of women around the country. I have not talked to anyone who said they were terrified, but I have read the hearings of last week, and I would guess they may be taking two pills now—first a tranquilizer and then the regular pill—because of our erudite investigation.

Looking at the pill on balance, then, do you think the disadvantages, based on a study of 21, which is not a very large group, outweigh possible advantages? How many are going to have a stroke who do not take the pill?

Dr. CLARK. I think you are really asking a question there, Senator, which requires several answers. This would be a very simple problem if this were the only known contraceptive agent. If we were to say to the female population—and the male population, who have a certain interest in this also—if we were to say, it is either give yourself up to reckless abandon or take the pill, the question would be much simpler, then, would it not? Because then it would be the hazards of one agent against another.

This is not entirely the case. There are a very considerable number of agents which will control reproduction. One cannot, I think, take out any one of these and look at it exclusively as if it were the only means of controlling reproduction.

Unfortunately, for my sins, I have been on a fair number of panels about this problem in the last year or two. Sooner or later, there is

always some idiot who gets up and says, would you give your own daughter the pill?

There are two sensible answers to that. The first is, my daughters are both college age now and they would not do anything I told them to anyway. The second answer, I think, is that in a survey such as this, one is dealing with statistics. These have to be looked at in the light of a group of other statistics. When you come down to a question of the patient, that patient is no longer a statistic.

If you were asked, would you give your wife or your daughter the pill, or would you not, one can only answer, this would depend upon circumstances.

If one felt that in the case of a given patient, the control of reproduction is essential for any of a variety of reasons, and that in the same patient, the only applicable method of controlling reproduction is to use the pill, obviously, you would use it. But if that were not the case, obviously, you would not. And I do not think that we can answer those questions at the moment, sir.

Senator DOLE. Well, would it be fair to say, as I have suggested in the statement I filed on January 14, that we might sort of rely on the doctor-patient relationship in most cases rather than on the Senators?

Dr. CLARK. I think that where the relationship between the patient and his or her physician is a good one, this remains the most reliable guide. However, one must be assured that this relationship is active and effective.

Senator DOLE. I concur in that. But again, would a study based on 21 be based on a representative sampling. Is such a number large enough or is it too small to be statistically meaningful?

Dr. CLARK. This reminds me of Mr. Thurber's answer with regard to the question about the health of his wife. He said, "Compared to what?"

Is it large enough for what? Is it large enough to determine whether there are particular features to these strokes that tend to distinguish them from other more commonly known strokes? It is large enough for that.

Is it large enough to decide whether this is a hazard to which we are exposing American women in vast numbers and they should be protected from it? No, not for a moment.

It is large enough to answer one question, but not the other.

Senator DOLE. I think that is important for the record. I think sometimes, we may read something into a statement that is not there.

The statistics indicate that there are great numbers of women taking the pill, and we have some obligation to develop a balanced record. Maybe we are going to find out that the pill should be abolished; certainly, we should do all we can on the Republican side to make certain proper regulations are followed, that the patients are informed, that the doctors are informed, and that it is as safe as can be made.

The last question, then, is: Based on your own case study and literature you have read, and conversations you have had with other experts in the area, do you generally feel that the disadvantages outweigh the advantages?

Dr. CLARK. Senator, as I have pointed out to you, I am a neurologist. I do not deal with these things, and furthermore, I regret to say that

the opinions of a man who has reached the time in life when sex is largely a hobby would, I fear, scarcely be accepted generally.

I can tell you a bit about strokes; I am not here to answer whether the pill should be abolished or kept.

Senator DOLE. Well, do you have any opinion on how the dangers of this contraceptive compare with other contraceptives?

Dr. CLARK. What dangers do you mean? If you mean the dangers of getting pregnant while feeling safe, this is an excellent contraceptive.

Senator DOLE. I understand the IUD's may cause cancer in some cases. I think a witness testified last week on the possibility that this may be more satisfactory from the standpoint of health, not pregnancy.

Dr. CLARK. I believe it is generally agreed at the present time that most of the forms of oral contraceptives now available, if taken according to directions, are about as effective a contraceptive, as reliable a contraceptive as the world has ever known, with the single exception of a firm and maintained "No." Without doubt, the hazards of purely mechanical devices such as a diaphragm, the medical hazards are less. But as one moves to these other forms or methods of contraception, medical hazards may be less but the reliability of the method is also less, so the hazard of an unwanted pregnancy becomes greater.

I must repeat, I am not able to estimate this.

Senator DOLE. No, I am not trying to say that you should or should not. I thought if you had any information, it would be helpful to us. I appreciate your testimony very much.

Thank you.

Senator NELSON. Thank you very much, Doctor, for taking the time from your busy schedule to come here and give us your testimony.

I might say that from the very beginning, the Chair has made it very clear, and in frequent statements over the past 3 years, that all viewpoints in a balanced fashion would be heard before the committee. In the implementation of that policy, I have invited regularly every drug company in the United States that manufactures the drugs discussed to come before this committee as a witness or suggest somebody; and, furthermore, that if any drug they may manufacture is discussed before the committee, they would get a priority to be heard ahead of any other witnesses we schedule. I stated that last week. I shall repeat it this week, that every manufacturer of the pill is entitled, as I have told them privately in talking to some of their representatives, and publicly here, is entitled to send a witness.

Some of them have suggested witnesses; they are on the witness list.

Now, I want to say further that one of the national magazines ran a story saying, as did Senator Dole, that the witnesses are 7 to 1 against the pill. That has not been the case at all. If you look down the list, I think you would say that Dr. Hugh Davis, director of the Contraceptive Clinic at Johns Hopkins, was a critic of the pill. He did not say, and neither has any other witness, that the pill should be removed from the marketplace.

Dr. David Carr was neither a proponent nor an opponent of the pill. He discussed the possible genetic effects. I would assume that scientists who have been invited here, such as the last one, who had studied side effects involving the pill, would give their scientific testimony so that the public, the committee, the press, the medical profes-

sion would have the best information there is available in this country.

Dr. Carr said nothing about whether he was for or against the pill. He discussed the possible genetic effects.

Dr. Marvin Legator, chief of the Cell Biology Branch and Director of Pharmacology and Toxicology, Bureau of Science, Food and Drug Administration, discussed the possible genetic effects and made it perfectly clear that these effects ought to be studied on all potent drugs. Everything he had to say involving the pill involved all potent drugs, and they are developing methods now that would make it possible to study the genetic effects.

I would assume this is the kind of scientific information we ought to gather. He was neither for nor against the pill.

Dr. James Whitelaw, O'Connor Hospital, San Jose, Calif., merely commented on the effect of the pill on sterility. He said he thought that, in prescribing the pill, the fertility of the woman ought to be proven first.

Dr. Roy Hertz, assistant medical director of the Bio-Medical Division, Population Council, Rockefeller University, New York, signed the FDA report and said he agreed with the summary of conclusions. Nevertheless, he was quite critical of the widespread use of the pill.

Dr. Kistner, a very distinguished obstetrician, of the Department of Obstetrics and Gynecology of Harvard Medical School, was a strong proponent of the pill.

Dr. Giles Bole of the Rackham Arthritis Research Unit, University of Michigan, simply discussed the possible arthritic side effects. He was neither for nor against the pill.

And Dr. Kassouf talked mainly on the advertising and promotion.

I would suppose if we were trying to keep a baseball count as to that first series, you might say two were against, though neither one of the two recommended the removal of the pill, and one for. Dr. Hugh Davis was not against the pill, he said he thought it ought to be used for the purpose of spacing pregnancies and probably a sustained use of 2 to 3 years ought to be the maximum.

So I just want to lay to rest the assertion made by a national magazine that they were stacked seven-to-one against the pill.

Now, let me say further, if there is a scientist in the United States, any scientist that any drug company can recommend, who has——

Senator DOLE. Do they have to be recommended by a drug company? Could I recommend one?

Senator NELSON. Yes, that has been well known to any other member of the Committee since the hearings started. Any company, any doctor, any scientist, any hospital, who has testimony that these side effects do not exist or are not important, we want to hear them. That has been my position and that of this committee from the beginning.

We shall also be hearing from Dr. Guttmacher, president of Planned Parenthood. We shall be hearing from General Draper of the Population Crisis Committee and others he suggested.

We shall be hearing from the Food and Drug Administration. We hope to hear from Dr. Egeberg and Secretary Finch. And, as I said, anybody else who has any credentials.

These will be balanced hearings. All viewpoints will be heard, and the Chair gets a little bit weary of the criticism that they are not going

to be heard. As I say, we welcome the suggestions of anybody to be heard who has any scientific knowledge that can be valuable to these hearings, to the scientists, to the medical profession, to the public, to the users of the pill.

Senator DOLE. Mr. Chairman?

Senator NELSON. Yes.

Senator DOLE. I certainly share in the views just expressed by the Chairman. I trust and I have reason to believe they will be balanced hearings. I do have suggestions here to make concerning additional witnesses.

Senator NELSON. We shall be glad to have them.

Senator DOLE. Let me say, as I said earlier, that I am neither anti-pill or pro-pill. In fact, I think the Chairman is in the same status. We are here to explore a very highly complex and technical controversial subject. We are not here to either crucify or defend or sensationalize, because this does affect, as I understand, some 8.5 million people in America.

As I have said before, as a new member of this committee, I plan to participate whenever possible, and I do hope that everybody who has an interest—not just the drug companies, but others—will have an opportunity to be heard, whether they have perhaps taken the pill, had adverse effects, have not taken the pill. I think, as the Chairman has stated this morning, the primary purpose of this hearing is to determine as much as we can about the safety of the pill because it does affect some 8.5 million women and their families, their lives.

And aside from the very serious sociological and cultural implications, we are dealing with the human reproductive system, which is one of the most complex and mysterious devices in the universe. So I certainly am here in that spirit, Mr. Chairman.

Senator NELSON. Thank you, Senator.

Senator Dole said he was neither for nor against the pill, and he assumed I am in the same position. I am not in the same position. I strongly favor the best conceivable pill that can be designed. I certainly hope we shall continue our research and improvement of the pill.

I think the unlimited growth of the population of the world is the most serious crisis the world faces, so I am not a critic of the contraceptive methods, and I hope we shall get a pill as near perfect as possible.

I would support appropriations for research to get a better pill and appropriations to get a better reporting system so that we shall gather all information about adverse effects. I will support the proposition, almost everybody else does, everybody before this committee, that the public is entitled to informed consent.

We called these hearings—before Dr. Ley, former Director of the FDA, made the statement that more information ought to be given to the women, before the FDA sent a letter just recently to the doctors of the country saying that the women ought to be better informed, and before the FDA sent notice today that the warning notices should be put into the package received by women—all of these things happened after these hearings commenced, and I think they are in the public interest.

Our next witness is Dr. Wood, Director of the Department of Medicine at Pennsylvania Hospital, Philadelphia. Pa., and Professor of Medicine, University of Pennsylvania.

Dr. Wood, the committee appreciates very much your taking the time to come here and testify today. You may present your testimony in any fashion you desire. If you wish to extemporize from your statement or elaborate on anything you have said, just proceed to do so. I assume you have no objections if a question occurs to Senator Dole or to myself in the course of your testimony, if we interrupt?

STATEMENT OF DR. J. EDWIN WOOD, DIRECTOR, DEPARTMENT OF MEDICINE, PENNSYLVANIA HOSPITAL, PHILADELPHIA, PA.

Dr. WOOD. No, please do.

Senator Nelson, did you want me to go ahead, sir?

Senator NELSON. Yes, proceed, Doctor.

Dr. WOOD. This is in respect to oral contraceptive drugs and blood-clotting.

The problem created by widespread use of oral contraceptive agents with respect to clotting of blood may be stated simply. I would like to take advantage of your comments and extemporize a bit here.

I use that comment in my opening sentence with respect to the matters of public policy. I think that the problem for scientists, of course, is very much broader than I shall state in the next few sentences. For example, the matter of stroke, as was brought out by the conversation with Senator Dole, is somewhat controversial.

It is certainly being debated by experts at the present time. Therefore, I have not included comments on this.

Going back, then, to the written comments, stating the problem simply, there is a minimum but definite hazard to life while using these drugs because of the side effect of causing blood to clot in the veins. The lethal effect of this clotting occurs as a result of movement of the clot from veins in the lower extremities to the circulation of the lung—a condition referred to as pulmonary embolism.

Apparently, the individual taking these medications is either unaware of this risk or only vaguely aware of it and usually rates the possibility as so unlikely as to require little consideration. The physician, though aware of the risk, experiences tremendous pressure from his patient to prescribe the medication, realizing that she can obtain these drugs elsewhere were he to refuse.

Ordinarily a medication whose benefits could be achieved in a safer way would experience little use by physicians. I am referring to medications of all sorts used by doctors. Alternately, a drug which appears at first to have great value, with use by physicians, but in fact does not, is used extensively for a brief period of weeks or months only. Oral contraceptive agents are an exception to this pattern because of the great positive public reaction to the agents.

Ordinarily the public has no reaction to a new form of medical therapy or the public reacts negatively. The point is, in my view, that public response has been partially responsible for the widespread use of oral contraceptive agents.

I might say parenthetically again, and with respect to the national magazine that Senator Nelson just referred to, physicians are not able to distinguish susceptible and individuals except in special circumstances, when the patient is not in good health. And this, in my view, is an exception. Most of the patients that utilize these agents are in good health and there is no way in the world that a doctor can tell which one will suffer from thrombophlebitis, for example, which is the condition I am talking about now, and undoubtedly others as well.

Going directly now to the question of blood-clotting in the veins, there are several lines of evidence that imply a definite risk of blood-clotting with use of oral contraceptive agents (1). First, a number of cases of thrombophlebitis with pulmonary embolism have been described in young women who did not have vein disease and who were not pregnant but who were taking oral contraceptive agents.

This kind of evidence is pertinent in that it would be considered extremely unusual for such a person to suffer this sequence of events. Thrombophlebitis ordinarily is seen in older patients who are bedridden, obese, suffering from cancer, suffering from heart failure, or in patients following surgery.

The second line of evidence is simply that of quantitative evaluation of the above general observation. It is the British studies which have already been referred to frequently in these hearings. Thus, careful studies of population groups have indicated that women taking oral contraceptive agents are eight times, or in fact more, depending on how you look at the data—are eight times more likely to suffer thrombophlebitis and pulmonary embolism than are comparable young women not taking these agents (2, 3).

Again parenthetically, many early studies neglected the fact that the instance of thrombophlebitis gradually increases with age and usually involves some other disorder. So we failed to compare completely normal young women taking the pill with completely normal young women not taking the pill.

A third line of evidence has to do with mechanisms whereby this unfortunate side effect of oral contraceptive therapy might take place. It is important to realize that in establishing a cause and effect relationship between an agent and a disorder, simple demonstration of association between the two is not enough. It is essential that some rational mechanism whereby the cause could lead to the effect be demonstrated.

The mechanism for causation of spontaneous thrombophlebitis—occurring independently of oral contraceptive agents—is not fully understood. However, a combination of data achieved through study of the kinds of patients described above, as well as data obtained in the laboratory, lead to several general conclusions.

First, one of the major contributing causes of thrombosis in veins appears to be that of reduced velocity of flow of blood in the veins or relative stagnation or stasis of flow in the veins.

A second factor of great importance in reproducing this disorder in animals, but very poorly understood in man, is that of the changes in

NOTE.—Numbered references at end of statement.

blood chemistry which would lead to an increased tendency of the blood to clot (4).

Studies of women taking oral contraceptive agents have yielded relatively unimpressive data with respect to changes in their clotting mechanisms; i.e., changes in blood chemical constituents that have to do with clotting.

This point is my own view, and I should have pointed out prior to this that I am not expert in the field of clotting, though I do a great deal of general medicine, so I have some interest in this field. In referring back to the question of clotting mechanisms in the person with thrombophlebitis. This is also true of patients who have thrombophlebitis in clinical circumstances completely independent of oral contraceptive agents.

Studies of women taking oral contraceptive agents have led to the clear-cut finding of dilatation of the veins of the extremities—other veins as well perhaps but they have not been studied. These dilated veins carry the same amount of blood as before but since they are wider in diameter the blood flows more slowly.

The net effect of this series of events is a slowing of the blood flow during oral contraceptive therapy. This finding is distinctly abnormal and is not observed in any other circumstance in young women except during pregnancy or in the presence of varicose veins.

Further, apropos of the cause and effect question described above, the finding establishes a clear-cut relationship between oral contraceptive agents and changes in the veins which could lead to thrombophlebitis and ultimately pulmonary embolism (5, 6, 7).

I have listed a few conclusions which, of course, are those that I have reached on the basis of the kind of information just presented.

First, in the view of this witness, oral contraceptive agents have a clear-cut risk to the user. Present status of these agents is such that there is widespread public acceptance and in fact by this time, reliance on these agents so that withdrawal from the market would be difficult to accomplish, and probably unreasonable.

2. The benefits of these agents are primarily in the sphere of psychological benefits and the sphere of convenience to the patient, thus it seems unwarranted to this witness to suggest that "benefits outweigh risks."

3. Part of the problem as it presently exists, occurs as a result of public pressure; thus, education of the public should be an important aspect of the national response to the problem.

Regarding earlier questions, inserts should state in simple, nonwordy language, that leg soreness, redness of the leg, swelling or cramps of the leg, may mean the presence of phlebitis, and the patient should consult the physician at once. Again parenthetically, I think most of the inserts have so many words that even physicians tend not to read them. It is very difficult to separate the important aspect of it by simply scanning it.

Senator NELSON. You were referring, however, to the package insert?

Dr. WOOD. Yes, sir.

Senator NELSON. The package insert only goes to the pharmacist or, unless it is a sample, to the doctor. Are you saying that the same information should go directly to the patient?

Dr. WOOD. Yes, I think that information should go to the patient and it should be in written form.

Senator NELSON. That would mean, would it not, that each package that the patient gets would necessarily include whatever explanation or indications for consulting the doctor or side effects you might include; is that right?

Dr. WOOD. Yes, sir.

Senator NELSON. One more question. In reading the literature and the package insert about the various symptoms that may occur, I would assume you would agree that for other reasons, it is important that the literature be in each package, because certainly we cannot expect the user to remember for 3, 4, or 5 years all these various indications and symptoms which should cause her to consult her doctor.

Dr. WOOD. That is correct.

No. 4. All of this information suggests that the oral contraceptive drugs were released for public use prematurely. Research on these drugs was far from complete at the time that they were released for public use. There is some evidence to suggest that oral contraceptive agents with reduced concentration of estrogenic compounds would be safer. Extensive, carefully planned research should be started at once to answer this question, in that it will take several years at least to achieve an answer. It is extremely unlikely in the view of this witness that presently available data, including those from the British study, will yield an answer. This is in respect to what combinations of compounds would be safest.

No. 5. The extensive cutback in general research funds in medicine and the concurrent worsening of the problem of population growth requires that funds be specifically earmarked for research in the sphere of finding the safest possible oral contraceptive agent.

(The references to Dr. Wood's statement, follow:)

REFERENCES

1. Wood, J. E.: Oral Contraceptives, Pregnancy, and the Veins. Editorial. Circulation 38, 1968.
2. Inman, W. H. W., and Vessey, M. P.: Investigation of deaths from pulmonary, coronary and cerebral thrombosis and embolism in women of child-bearing age. Brit. Med. J. 2: 193, 1968.
3. Vessey, M. P., and Doll, R.: Investigation of relation between use of oral contraceptives and thromoembolic disease. Brit. Med. J. 2: 199, 1968.
4. Wessler, S.: Studies in intravascular coagulation: III. Pathogenesis of serum-induced venous thrombosis. J. Clin. Invest. 34: 647, 1955.
5. Wood, J. Edwin: The Veins. Boston, Little Brown and Co., 1965.
6. Goodrich, S. M., and Wood, J. E.: Peripheral venous distensibility and velocity of venous blood flow during pregnancy or during oral contraceptive therapy. Amer. J. Obstet. Gynec. 90: 740, 1964.
7. Goodrich, S. M., and Wood, J. E.: Effect of estradiol 17 β on peripheral venous blood flow. Amer. J. Obstet. Gynec. 96: 407, 1966.

Senator NELSON. Is there, in your judgment, any difference between the use of the pill that extends over a long period vis-a-vis a short period? As I recall, Dr. Hugh Davis, of Johns Hopkins felt that the pill, if used at all, should be used to space pregnancies over a period not longer than 2 years, vis-a-vis over a 15-year period.

Do you have any viewpoint on that?

Dr. WOOD. Well, one point of information with respect to this question is that the chance for thrombophlebitis is greater in older women,

and the arbitrary age of 35 has been selected, and it gradually goes up with the years. It is presumed that this is not due to a cumulative effect of the pill over the years, but simply a risk that has to do with aging.

Our data, studying the effect of the pill on the circulation of the extremities, have indicated that there is no difference in the effect during the first several months of use of the pill and in use of the pill for a year or two. This does not, however, lead to any conclusion as to what substantially longer periods of time, 5 or 10 years, would mean. We just do not have that information at all, and it is a matter for research.

I think that the thing that has concerned us most, which is not a lethal hazard, is that there is the potential for continued dilatation of the veins so that they would not return to their original status. There seems to be the cosmetic hazard of varicose veins on a permanent basis. But there is no way of knowing this except long-term study.

Senator NELSON. Thank you very much, Doctor.

Senator Dole?

Senator DOLE. Just briefly.

In your conclusions, Dr. Wood, you indicate first of all that because of the pill's widespread acceptance, it would probably be difficult to gage the possible effect of withdrawal of the pill from the market?

Dr. WOOD. Yes.

Senator DOLE. Then in reference to suggestion No. 4, that perhaps the contraceptive drugs were released for public use prematurely—you are suggesting there, as I understand it, that there be continued research to find the safest possible pill.

Basically, that is what you say in suggestion No. 4.

Additionally, I think you have made a good suggestion about the pill labeling information. But, of course, as the chairman pointed out, this is all directed to the doctor, the physician. And even if it were available to the patient, I am certain that there would be much in the label that would be misunderstood or not understood at all.

Are you suggesting that there be some written information accompanying the prescription to the patient? Or how do we get the information to the patient most effectively?

Dr. WOOD. Well, I cannot, of course, describe an adequate label as I sit here. But the guidelines, it seems to me, should be that there should be written material with the agents for the patient to read.

Second, I think that we should see that the written material is not so complexly stated, either because of medical language or simply because of its length, that the patient could not keep it all in mind.

I further believe that the hazards to the patient are not that extensive. I believe the ones such as the one I talked about this morning that are now developing are very clear cut, can be described in a way that the patient can understand.

Of course, if she has pulmonary embolism, that is something that a label cannot protect her against. But the majority of the patients get thrombophlebitis, and they are aware of it and delay seeing their physician because they are not exactly sure what it is.

Senator DOLE. Of course, it is very dangerous. But I certainly share that recommendation that there should be some information available that can be understood, that is brief and to the point and that everybody can understand.

I assume this would be in addition to anything the doctor may tell the patient in the first instance, because sometimes things are forgotten, and also the doctor may not have time to cover everything he should.

That is all.

Senator NELSON. Doctor, could you either submit or just give us a brief biographical background of your experience in addition to your title?

Dr. WOOD. Would you like me to do that now?

Senator NELSON. Fine.

Dr. WOOD. I graduated from Harvard Medical School in 1949, worked at Boston University in cardiovascular research, including a stint in the military service—also in cardiovascular research—for about 10 years.

I then have held successive academic positions, again in research, particularly in the area of the vascular system, at the Medical College of Georgia, the University of Georgia, and have recently accepted my present post at the University of Pennsylvania.

Senator NELSON. Thank you very much.

There is one question from the minority counsel.

Mr. DUFFY. Just one question, Doctor.

Perhaps I did not hear you correctly, but you added something to your first conclusion that was not in your written statement. Did you say that it is probably unreasonable to withdraw the pill from the market?

Dr. WOOD. Yes. I do not recommend that. I think I probably should have dilated on that a little bit. I think it is a useful medication and I think it should continue to be available to the physician and to his patients. We should work as rapidly as possible toward getting the very best and safe medication possible.

Mr. DUFFY. Thank you.

Senator NELSON. Thank you very much, Doctor. We appreciate your taking the time to come.

Our next witness is Dr. John Laragh, professor of clinical medicine, Columbia University College of Physicians and Surgeons, and attending physician at the Presbyterian Hospital, New York City.

Dr. Laragh, the committee is pleased that you were willing to take the time from your busy schedule to come here today to testify. You may elaborate on your submitted statement as you please.

STATEMENT OF DR. JOHN H. LARAGH, PROFESSOR OF CLINICAL MEDICINE, COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS; AND ATTENDING PHYSICIAN, PRESBYTERIAN HOSPITAL, NEW YORK CITY

Dr. LARAGH. Thank you, Senator.

I am very pleased to be here.

I am, as you indicated, a professor of clinical medicine at Columbia University in New York City and also attending physician at the Presbyterian Hospital.

Senator NELSON. Would you, just for the record, give a brief biographical sketch on your professional background?

Dr. LARAGH. Yes, sir.

I was graduated from Cornell University Medical School in 1948. After serving my internship and residency at the Presbyterian Hospital, I have remained there on the teaching and research staff of the department of medicine ever since.

I am actively engaged in the clinical practice of medicine, and I am a physician with board certification in internal medicine.

Senator NELSON. You are actively practicing medicine with patients?

Dr. LARAGH. Yes, I am. I am a physician in practice practicing internal medicine.

Senator NELSON. And this is a teaching hospital?

Dr. LARAGH. At a teaching hospital. I am the director of the Hypertension and Nephritis Clinic of the Presbyterian Hospital, and for 8 or 10 years have been a consultant to the U.S. Public Health Service for cardiovascular disease.

I am also chairman of the Council for High Blood Pressure Research of the American Heart Association. I consider myself a physician who not only practices medicine but who is a medical researcher and educator.

Senator NELSON. Thank you.

Dr. LARAGH. In my comment to you this morning, Senator, I would like to tell you about some studies that we have made which have established clearly a relationship between the use of oral contraceptive drugs and the development of high blood pressure. This relationship came to us by chance in the course of making clinical observations on our patients sometime in 1966, when we observed a woman who we knew had normal blood pressure develop rather severe and impressive hypertension several months after starting an oral contraceptive medication.

Armed with this observation, which we recognized at first could be purely coincidence, and I would emphasize that possibility, because so many million people are taking the pill and so many million women have high blood pressure that the two phenomena could certainly be coincidental. But we were able to collect some eight patients with a similar relationship—that is, the story of no known hypertension prior to the pill, development of hypertension on the pill, and in six of these——

Senator NELSON. They had a physical examination report that showed there was no hypertension before they took the pill?

Dr. LARAGH. Yes. Well, as with all clinical studies, all of them had not been examined by us personally before that, but their histories and their backgrounds indicated that most of them had not had high blood pressure before the pill—six of them, I think, six out of nine. And the histories were fairly reliable in most cases.

Even this observation is, of course, subject to chance occurrence with the two situations being so common. However, we withdrew the medication from nine patients, and six of them had a dramatic improvement in blood pressure. In brief, the blood pressure came back to normal.

Senator NELSON. Now, six of them had no prior history; three of them did?

Dr. LARAGH. The way it breaks down, these numbers—let's get it straight for the record. I have them here.

Actually, the absolute numbers are not so important as the point. But we have nine patients in whom we withdrew the medication. In three, the blood pressure came back to normal. In three, the blood pressure greatly improved. The last remaining three, the blood pressure stayed high.

Senator NELSON. Which of those groups had a prior history of hypertension?

Dr. LARAGH. Five of them had hypertension which was known prior to taking the pill.

Senator NELSON. Of those five, what happened when the use of the pill was terminated?

Dr. LARAGH. Of those five, three of them improved.

Senator NELSON. Will you explain the significance, then, of these statistics?

Dr. LARAGH. Well, first of all, these numbers are much too small, Senator, to have statistical significance. But maybe as I develop the story, you will see why I think the connection of a cause-and-effect relationship has been established.

What we did, having observed that three became normalized, three greatly improved, and three remained unchanged of the nine that we stopped the medicine in, two of the women wanted to go on with the pill, for obvious reasons, and we decided on what we call a rechallenge trial, since there was no evidence prior to this that hypertension would be any risk. In both of these women, when we gave the pill again, the hypertension would be reproduced and then, on withdrawing the pill, the hypertension disappeared again.

Senator DOLE. Would you have observed the same results had these women been pregnant?

Dr. LARAGH. What would happen had these women become pregnant?

Senator DOLE. Would you have observed the same results of your study as a result of normal pregnancy?

Dr. LARAGH. I am not sure that I—maybe you had better set up the model so that I can understand it.

Senator NELSON. I think the question he is raising is whether the introduction of the estrogens as a consequence of pregnancy would have caused these women to get hypertension in a fashion similar to that from the artificial causes?

Dr. LARAGH. I cannot tell you about these particular women, but what I can tell you generally, Senator Dole, is that it is a well-known fact—I think no one has exact figures because it is a epidemiological figure, but some 10 percent of all women develop high blood pressure during pregnancy, something of that order. So that the relationship is not really a surprising one if you appreciate that we are producing chemical pregnancy in the hormonal sense. It almost would be more surprising if nobody ever got hypertension, because hypertension is a recognized complication of pregnancy.

It usually goes away on cessation of the pregnancy, just as it seems to go away on cessation of the pill.

Senator DOLE. So the results are not necessarily surprising?

Dr. LARAGH. No, they are not surprising. But I would say that, like the evolution of knowledge with many other drugs, the usage of the

drug goes on for many, many years before perhaps an important finding like this is revealed.

Senator DOLE. Thank you.

Senator NELSON. Of those three who had hypertension when they were taking the pill and it disappeared upon return to normal afterward, had any of those had a history of hypertension?

Dr. LARAGH. No. None of those did.

The rechallenge experiment is what made us most suspicious of the cause and effect relationship. I think what supports it most strongly is the fact that since our reports, groups all over the world—I do not have exact figures, but I can say that perhaps at least 50 such experiences have been reported in the literature by other medical groups. So I do not think there is any question about the fact that in certain rare situations, fortunately rare, this can be a side effect or a consequence or a toxic effect of the use of these hormones.

Our next step, since I am, as I indicated, not a gynecologist, but a physician who studies high blood pressure, our next step was to measure certain components of the kidney adrenal hormonal system which we are interested in, and which we have found to have an important connection with the causes of all high blood pressure. We found that when you feed or administer oral contraceptive agents to these women, you produce in all of them an enormous increase in a chemical known as the renin substrate which circulates in the blood. This substance has the capacity to release angiotensin, a hormone which is the most powerful of all hormones in its capacity to raise the blood pressure.

The observations, then, revealed that the use of oral contraceptive agents produced a striking deformity of this blood pressure hormone system involving the kidneys and adrenal glands, a hormonal system which regulates the blood pressure in all of us and which regulates the blood pressure through regulating the amount of salt in the body—you all know that there is a well-known connection between salt and blood pressure and these hormones which cause salt retention and are implicating other kinds of high blood pressure.

It is also well known that women taking these oral contraceptives—some of them, at least—swell up and accumulate salt and water. Probably this occurs through activation of the renin angiotensin hormonal system which regulates the amount of salt in the body of all of us.

So that we have some chemical explanation or basis for why the oral contraceptives might cause hypertension in certain women. The observations of this sort, I think, are given increasing relevance by, first of all, what Senator Dole indicated that it may provide us with an analog of the experience during natural pregnancy, where hypertension is well known to occur.

Secondly, there may be other situations in which hormones, female hormones, are used, such as in the treatment of prostatic cancer, where hypertension may also have been induced, or even in the treatment of the menopause. So that this effect has, is expressed or is fulfilled in other areas where estrogens are used.

I would express, however, that while we do not have accurate epidemiological figures, and as you have heard from many speakers, these are indeed hard or almost impossible to come by. This effect of the oral contraceptives is a rare one and it does not occur in a large majority of women who are taking the pill.

We, of course, are interested, everybody is interested to know what might be the sensitizing situation so that you can anticipate which women might get hypertension. We do not have any firm clues. But it does look as though those who accumulate salt and water and gain weight on the oral contraceptives might be especially vulnerable; also those who have underlying kidney diseases might be especially vulnerable.

The comforting thing thus far about the observation is the fact that on stopping the pill, from 2 to 8 months later, the hypertension goes away in most cases. In the ones that we have observed, anyway. So that it is a reversible thing so far.

I think the means of dealing with it is to insist, or as has been emphasized in other aspects of this hearing, to fully disclose new observations like this as the first step; full education—and education, unfortunately, is a continuing process. You can tell somebody something last year and they do not remember it this year, so that you cannot repeat these facts often enough.

They should be in conspicuous places, as some people have indicated, in the package circular, and elsewhere.

I think the advice we would give tentatively would be that, in using the oral contraceptive pills, the blood pressure be checked every 3 months, something which probably was not done systematically in the very beginning, perhaps because the pills are given primarily by gynecologists, perhaps because hypertension was not anticipated.

Senator NELSON. May I interrupt?

Dr. LARAGH. Yes.

Senator NELSON. You are suggesting that the blood pressure should be taken once every 3 months?

Dr. LARAGH. About every 2 or 3 months, yes.

Senator NELSON. We have had other testimony—in fact, I think all witnesses, whether they were somewhat or very critical of the pill, or in support of the pill, commented upon the importance of a physical examination once, at least, every 6 to 12 months, with a Pap smear, and so forth. Are you saying that you believe that that is too long a period?

Dr. LARAGH. That is much too long for the blood pressure, because you ought to know about it. It takes 1 minute, or a few minutes, to take the blood pressure, and somebody might have had it a whole year if you did that, in my opinion. I would recommend every 2 or 3 months.

Perhaps a Pap smear is another matter, but I would certainly favor having the blood pressure checked every 3 months.

Senator NELSON. But would you consider that—I am just trying to get your judgment—as the nearly perfect procedure? Would you consider it a serious matter if it were once every 6 months?

Dr. LARAGH. I would think that the logistics of taking the blood pressure are so simple that I would take it every 3 months.

Senator NELSON. The logistics are that you cannot find a place to park the car.

Dr. LARAGH. That is right. Well, we have a responsibility when we have our powerful drugs like this; our responsibility is to learn about them, and the second responsibility is to apply the information. Otherwise, we do not have any right to have them on the market.

I believe strongly that they should be on the market, but I believe that as new knowledge is revealed and developed and exposed by people such as yourself, we have a mandate to operate from the new base of knowledge, modify our approach, and continue to modify it all the time as we learn more.

I do not think any drug can ever be completely studied before it is released. Certainly, this drug was studied much more extensively than almost any. Yet the history of powerful drugs simply reveals for us that sometimes, 8 or 10 years go by before a very serious side effect is appreciated. You cannot set up animal models to anticipate all of these things, and in a drug like the oral contraceptive, we have a very unique situation, because this is a mass population experiment in this sense, in which healthy people are taking the pill in large numbers.

Secondly, we have never had a medication in which the commitment for its usage might be daily for 20 years. There is no way that an animal model can answer this.

I think we just have to have great respect for what we are doing and set up devices so that we have very good detection systems, very good disclosure systems, and we continue to modify our usage.

At the same time, this accumulating information will help us in your goal, Senator, to realize what is wrong with the pill, and that is the first step toward developing a better one. I think we certainly have to search for better chemical methods, we have to search for methods which may reduce the dosage, for methods that may allow us to use the male as well as the female.

We have to compare the values of these compounds with mechanical devices.

Senator DOLE. Doctor, if you were going to inform a patient——

Senator NELSON. May I interrupt just one second? I have an amendment pending on the floor which will be taken up on a limited time debate at 11:30. I asked Senator Dole if he would be kind enough to complete the hearing.

I want to thank you very much for coming this morning, Doctor.

Dr. LARAGH. Thank you very much, Senator.

Senator DOLE (presiding). I am just wondering how you would state what you have stated to the committee in a very concise and effective way to a patient so that she would understand what you are telling us in a sort of complicated way.

Dr. LARAGH. Yes.

Senator DOLE. What would you put on the label for the patient, based on your study?

Dr. LARAGH. I think, Senator Dole, I think the situation has to be based—this situation and analogous situations—with many others, that are occurring all the time with many other powerful chemicals that doctors and environmental specialists now have available. It can only be solved by full disclosure on both sides. I think that our patient now has to participate in the decision in a different manner than he did perhaps 20 years ago.

In the final analysis, in considering whether a patient should use an oral contraceptive, the decision should be a value judgment that the physician makes with each individual patient. And this decision-

making capacity is the essence of the role of a physician. It is a quality that we call clinical judgment. It is a measurable capacity to weigh all the variables for the individual patient.

The way that you weigh the variables is you consider first of all the medical status of the patient, the age of the patient, the psychological factors involved in the patient's situations. She may have nine children or none, which would certainly vary your attitude.

In addition to all the medical and psychological and physical considerations involved in the individual, you then have to take into account sociological factors. The population explosion is a serious problem. Pregnancy itself has a risk. And the doctor and the patient, both together, cognizant of these risks, must make the judgment as to whether or not to use them.

I think you cannot have recriminations when one person in a thousand, or whatever the rare case is, has phlebitis or a stroke. You will not have recriminations when the essence of the information is the point of departure in the beginning.

As you point out, full disclosure and consent, and all these words are nice words that you and I like to use. But getting the message across to someone who is not as oriented as we are medically, even though you may try, is not a perfect art.

I think we have to do everything we can to simplify communication, to use education, to use techniques of repetition, to simplify the package insert. We can only go ahead in this area, and with many other powerful drugs, by using the knowledge positively and by full disclosure.

Senator DOLE. I think it has been pointed out by counsel that the FDA is moving in this direction, as indicated in their letter of January 12. The only thing that concerns me because I do not have all the expertise in this area, and I am not certain how many of the 8.5 million of the recipients of the pill may have, what do we put on it? I think it is a good idea to inform them through the doctor-patient relationships and perhaps by other means.

If we end up with a long list of things the pill may cause, how do we get the message to the patient?

In your case, you might say, the pill may cause high blood pressure, correct?

Dr. LARAGH. I would say that this is a rare—the incidence we do not have. We are dealing in frequencies. We are dealing in risks which are small. And I think there is a great danger, as you indicate, in scaring or alarming people while we are trying to digest the information ourselves.

Senator DOLE. And as you say, the patient must make a value judgment, and she has to consider all the factors. I assume somewhere along the line, we have to draw a line and say these are minimal and these are maximal.

I just wonder where you say your suggestion might fit in that picture, because pregnancy might cause hypertension. I think you indicate that as a very predictable result of your study.

But at the same time, I think we have some obligation to make a full disclosure to the user. I am just wondering as a matter of practical information, how can the patient ever make the value judgment if we confound her with so many different things that may happen? Where do we draw the line?

Dr. LARAGH. Yes. I think we have to admit all of the things that can go wrong. But I think we have to admit that the high blood pressure thing, just as I am sure the thrombophlebitis business and all of the things we are talking about, collectively, are a very low order of frequency. They constitute a very low order of frequency. As we get more knowledgable, we may correct this next year. Right now, it looks like it is rare, and in our high blood pressure case, it looks like we know how to deal with it.

So we admit it can happen, but I think we can also state that we know how to deal with it, and that it is very rare.

I think conceptually, you and I might not like the idea, but it has this potential, and we might search for better methods at the same time.

But I do not think we condemn a medication which serves a purpose when we have so many toxins in the environment that are just as dangerous, such as smoking, which do not serve any purpose.

So I think this again comes into the equation of making a value judgment.

Senator DOLE. I have no further questions.

Senator McIntyre just entered the hearing room. If he has no questions, the hearings will be resumed tomorrow morning.

Senator MCINTYRE. I have no questions.

Senator DOLE. Senator, we have only had three witnesses and they have been very helpful. Senator Nelson just left for the floor.

Thank you very much, Doctor.

(The summary statement and supplemental information submitted by Dr. Laragh follows:)

SUMMARY STATEMENT OF DR. JOHN H. LARAGH, PROFESSOR OF CLINICAL MEDICINE, COLUMBIA UNIVERSITY, COLLEGE OF PHYSICIANS AND SURGEONS; AND ATTENDING PHYSICIAN, PRESBYTERIAN HOSPITAL, NEW YORK CITY

ORAL CONTRACEPTIVES AND HIGH BLOOD PRESSURE

In the last several years a relationship has been clearly established for certain human subjects between the use of oral contraceptives and the development or enhancement of high blood pressure.

The results of these studies were published in the Journal of the American Medical Association (1967) and in the American Journal of Obstetrics and Gynecology (1968).

In our original study, the development or enhancement of high blood pressure was observed in eight patients who had been taking various oral contraceptive preparations. Furthermore, in six of eight patients who stopped taking the medication, marked improvement or complete correction of the hypertension occurred. In two of the patients, with a second trial of treatment, hypertension again appeared and then disappeared with the cessation of therapy. The studies point to the strong possibility of a cause and effect relationship between the use of these pills and the induction of serious hypertension in certain rare but especially susceptible individuals. Since these original studies additional similar observations have been made in our clinic and the findings have been widely confirmed by reports from other clinics throughout the world.

The factors which might sensitize a person to the pressor effects of these drugs remain incompletely defined. However, our studies suggest that the effect may be related to the marked changes observed in these patients in certain components of the renin-angiotensin-aldosterone system, a hormonal system which acts to regulate the amount of salt and water in the body.

The oral contraceptive medications consistently produce very large increases in plasma renin substrate concentration. Less consistent increases in plasma renin and urinary aldosterone were found. These changes can lead to an increased formation of angiotensin in the blood. Angiotensin is the most powerful substance known in its capacity to raise the blood pressure by constricting blood vessels. In certain susceptible individuals these induced hormonal changes with secondarily induced changes in sodium and water metabolism can operate to compromise the buffer capacity of the renin-angiotensin-aldosterone system which normally functions to regulate blood pressure and the salt and water content of the body.

When the buffer capacity of this hormone system is so deformed hypertension may be produced by very exaggerated (pressor) responses to circulating renin as it is released by various physiologic stimuli.

These observations may be relevant to the use of female hormones in other clinical situations. For example: a higher incidence of strokes has been reported in males receiving female hormones for treatment of prostatic cancer. They may also be applicable to the understanding of other forms of high blood pressure, particularly the hypertension which can occur spontaneously during pregnancy and seriously complicate its course.

In an individual patient, the determination of whether these powerful hormones should be used depends on a consideration of this and other known risk factors as balanced against the alternate risks inherent in pregnancy, and also the consequent hazards of overpopulation.

Since pill hypertension has been shown to be reversible, the hazards of serious high blood pressure during therapy can be avoided by regular checkups with appropriately oriented medical personnel. Education of these personnel and of the public is probably the most important factor for control of this undesirable side effect due to the pill.

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Oral Contraceptives

Renin, Aldosterone, and High Blood Pressure

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A relationship was established between the institution of oral contraceptive therapy and the development or enhancement of high blood pressure in eight of 11 patients. In six of eight patients who stopped taking medication, marked improvement or complete correction of hypertension occurred. In two patients, with a second trial of treatment, hypertension again appeared and disappeared. Oral contraceptive therapy produced impressive abnormalities in renin-substrate concentration and in its reactivity to exogenous renin as well as in endogenous renin activity and aldosterone excretion. The relevance of these abnormalities to the development of hypertension is not clear because similar effects occur in treated normotensive women. Further study of a possible connection between excesses of estrogenic and progestogenic substances, renin, aldosterone, and hypertension seems warranted.

This communication stems from clinical observations, made in certain hypertensive patients, which raise the possibility of a cause-and-effect relationship between the use of oral contraceptive therapy and either the development or the enhancement of arterial hypertension. Because of the widespread use of oral contraceptives, it seems likely that, in the large majority of patients, these medications do not induce an increased blood pressure. However, observations in 11 patients suggest the possibility that in exceptional circumstances these medications may be critically involved in the production of hypertensive disease. Five of the patients were regular members of our Nephritis-Hypertension Clinic; six others were referred from outside sources.

Six of the 11 patients observed were known to have been normotensive prior to the institution of an oral contraceptive regimen, and in four of nine patients who have discontinued medication, blood pressures have returned to normal or have improved. Furthermore, in two patients who had preexisting hypertension, withdrawal of the hormonal therapy was followed by a marked improvement in hypertension. Perhaps of special relevance to the proposed relationship are the additional observations that the administration of oral contraceptives produced very striking increases in renin-substrate levels and that these increases were frequently accompanied by abnormalities in aldosterone excretion and serum renin levels.

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Methods and Materials

Eleven women with high blood pressure were observed. Their ages ranged from 30 to 49. Using previously defined criteria,[1] we classified eight women as having uncomplicated benign "essential" hypertension, two as having renal hypertension, and one as having advanced hypertension. In addition to a complete history, physical examination, and routine laboratory work-up, all patients were repeatedly tested for abnormalities in plasma electrolytes. Renal function was evaluated by rapid-sequence pyelography[2] in all 11 and by renal arteriography in four. Three of the patients (No. 2, 6, and 11) were admitted to the metabolism ward and were studied by the use of controlled conditions of electrolyte and metabolism balance. None of the patients included in the study had been taking medications other than the oral contraceptives, except for the use of occasional sedatives. All patients had unrestricted diets, except for carbohydrate restriction in one with diabetes.

Aldosterone secretion or excretion rates were measured by a double-isotope dilution technique previously described.[1,3] Blood samples for estimation of renin were taken at noon, when the patients had been ambulatory for about four hours. Renin activity, renin-substrate concentration, and the rate of angiotensin formation in response to a fixed amount of exogenous renin were all measured by slight modification of the method of Pickens et al.[4] Serum was used rather than heparinized plasma because heparin inhibits the in vitro reaction of renin with its substrate.[5] Blood was drawn into tubes which were chilled immediately after collection. Rapid coagulation was achieved by the addition of 17 units of thrombin per milliliter. Highly purified angiotonase-free renin was prepared from human kidneys according to the eight-step procedure of Haas.[6] Techniques used for measurement of urine and plasma electrolytes have been previously reported.[1]

In normal subjects, both aldosterone secretion or excretion rates and the level of serum renin activity fluctuate as inverse functions of the state of sodium balance. Therefore, to identify abnormalities, all such measurements must be evaluated in relation to the dietary sodium intake or the rate of urinary sodium excretion. In normal subjects, the latter value closely reflects the salt intake. Nomograms of this relationship have been published.[1,7] It may be stated here that the mean aldosterone excretion rate is 19.8μg/day when the daily rate of urinary sodium excretion ranges from 60 to 120

mEq. With sodium excretion rates in excess of 120 mEq/day, mean aldosterone excretion is 14.6μg/day. In ambulatory subjects, the midday serum renin levels range from 2.7 to 10.4 mμg/ml for four hours of incubation (mean: 6.5 mμg/ml) when the sodium excretion rates range from 40 to 120 mEq/day. With salt excretion rates in excess of 120 mEq/day, renin levels range from 2.1 to 4.4 mμg/ml for four hours of incubation (mean: 3.2 mμg/ml). With sodium depletion, as evidenced by a urinary sodium content of less than 40 mEq/day, both aldosterone and renin can increase to much higher levels. The serum renin-substrate concentration normally ranges from 500 to 1,500 mμg/ml with a mean value of 1,000 mμg of angiotensin formed per ml.

Results

The association of oral contraceptive therapy with changes in blood pressure, aldosterone excretion, sodium excretion, renin and renin-substrate levels is summarized in the Table.

Effects on Arterial Blood Pressure.—The first four patients were known to have had hypertension prior to the initiation of oral contraceptives. Withdrawal of medication in patient 1 did not have any apparent effect on the degree of hypertension. In patient 3, slight improvement was observed. Cessation of therapy in patient 4 was associated with a striking return of her arterial blood pressure to normal levels. Patients 5 to 10 were all known to have been normotensive prior to the institution of hormonal therapy. After the medication was stopped in patients 6 to 10, blood pressures returned to normal patients 8 and 10) or improved (patients 6, 7, and 9) in a period of from three weeks to three months. Four months later, blood pressure was again elevated in patient 6. Patients 8 and 9 are of special interest because severe hypertension was first noted after institution of oral contraceptive regimens. The abnormality greatly improved in both after cessation of therapy. Furthermore, in both, resumption of therapy with another contraceptive preparation was associated with the reappearance of impressive hypertension, which again disappeared after terminating the treatment. Patient 11, who was known to be hypertensive for ten years, was given norethynodrel with mestranol (Enovid) 10 mg daily for 19 days while maintained on a constant regimen of the metabolism ward. No symptoms were observed, and blood pressure was not adversely affected, except for a transient slight rise noted on the third day of treatment.

Effects on Aldosterone Secretion or Excretion.—Maintenance therapy with estrogen and progestogen was associated with an abnormally increased aldosterone excretion rate in four out of the eight patients in whom it was studied (patients 1, 2, 6, and 8). In patients 1, 6, and 8, cessation of therapy was associated with the return of aldosterone excretion rates to the normal range. In patient 2, the marked oversecretion of aldosterone observed may well be attributable, at least in part, to severe, preexisting hypertensive disease. Patients 3 and 4 repeatedly exhibited normal aldosterone excretion rates while being maintained on hormonal therapy.

Effect on Renin-Substrate Concentration.—In nine of the ten patients in whom the measurements were made, the administration of birth control pills was associated with very striking and sustained increases in the concentration of renin-substrate in the serum, ranging from 1,980 to 8,650 mμg/ml. Only in patient 3 were no significant changes observed. However, this patient's hypertensive disease was complicated by the concurrent appearance of thyrotoxicosis. This feature may be related to the singular failure of this patient to exhibit any abnormalities in renin or aldosterone metabolism. Observations in patients 4, 6, 7-9, and 11 indicate that the increased renin-substrate levels can develop a few days after treatment is started and can persist for as long as four weeks or more after cessation of the therapy.

Evaluation of Serum Reactivity to Exogenous Renin.—Because of the very high concentrations of renin-substrate observed in these patients, an effort was made to evaluate the relative capacity of serum, containing increased amounts of substrate, to form the pressor substance, angiotensin. This was accomplished by employing an in vitro system in which a fixed amount of purified human renin was added to the serum in question, and its capacity to form angiotensin in a four-hour incubation was determined. The values were compared with results obtained from the study of the same subjects after correction of the renin-substrate abnormalities had occurred following cessation of therapy. The results of these studies (Table) demonstrate that the increased concentration of renin-substrate is uniformly associated with an increased capacity to form the pressor agent, angiotensin, when a standard concentration of exogenous renin is presented to the system. These observations indicate that, in the presence of an increased renin-substrate concentration, less renin would be required to release a given amount of angiotensin.

Effects on Endogenous Serum Renin Activity.—Because practically all methods for evaluating serum renin activity are based on the yield of angiotensin obtained after plasma incubation in which the endogenous substrate is the only source of angiotensin, one might expect that the patients with markedly elevated substrate levels would exhibit, ceteris paribus, relatively higher values for renin activity. In fact, serum renin activity was uniformly normal in four patients (No. 1, 3, 7, and 9) and abnormal in four (No. 2 and 4-6). In two other patients (No. 8 and 11), the values were at times elevated. This latter observation raises the possibility that abnormalities in renin activity might perhaps be more often demonstrable with more frequent sampling. This idea is supported by the serial studies made in patients 8 and 11. In

Data on 11 Women Taking Oral Contraceptives

Patient	Age	Diagnosis	Regimen, Dates	Blood Pressure (mm Hg)	Aldosterone Excretion (μg/day)	Urinary Sodium Excretion Rates (mEq/day)	Serum Renin Activity (mμg Angiotensin per ml for 4 hr Incubation)	Serum Renin-Substrate (mμg Angiotensin Generated per ml)	Substrate Reactivity (mμg/ml)	Clinical Information
1	44	Essential hypertension	(Ortho-Novum 10 mg for 2 yr)							Hypertension 7 yr. No change in hypertension off pill.
			11/30/64 (Day 12)	160/112	41*	67	5.8	3,785	80	
			9/3/65 (Off 7 mo)	...	14	128	5.2	1,085	30	
2	34	Advanced hypertension	(Enovid 10 mg since 1/64)							Hypertension known since 1959–during pregnancy. Grade 3 retinopathy. Hypokalemic alkalosis. Normal renal function continues on contraceptive therapy.
			8/19/64 (Day 5)	230/140	610 SR†	92	16.7	6,350	80	
			9/2/64 (Day 19)	230/140	508 SR	79	10.6	8,650	86	
3	38	Essential hypertension	(Enovid for 3 yr)							Hypertension known for 5 yr. Thyrotoxicosis developed 6/66. BP appears higher during contraceptive therapy.
			5/19/66 (Off 10 days)	200/110	...	...	1.6	875	44	
			7/19/66 (Off 2 mo)	145/100	5.1	85	3.6	635	31	
			(Resume Enovid 7/21/66)							
			9/13/66 (Day 4)	170/105	6.5	149	1.8	1,145	47	
			10/14/66 (Day 5)	180/110	4.4	118	1.2	920	36	
4	34	Renal hypertension	(Ortho-Novum 2 mg since 2/65)							Renal hypertension known since 1964–during fourth pregnancy. Had right nephrectomy, 1963, for kidney infection. Proteinuria 2+; BUN level normal. BP remarkably improved on stopping contraceptive therapy as aldosterone, renin-substrate, and substrate reactivity return to normal levels.
			9/16/65 (Day 17)	180/105	9.9	56	9.9	4,100	...	
			9/22/65 (Off 3 days)	180/110	6.3	300	8	3,300	...	
			10/10/66 (Stopped 10/11)	180/110	9.4	72	7.5	4,550	63	
			11/14/66	130/80	9.1	110	6.0	1,725	40	
			1/10/67	130/80	...	...	1.4	940	43	
5	49	Essential hypertension	(Enovid E 2.5 mg for 3 yr)							BP repeatedly normal prior to start of Enovid. Continues on medication.
			6/24/65 (Day 12)	180/105	21	121	28	8,085	...	
6	30	Essential hypertension	(Enovid E; 3/65 to 8/10/66)							Hypertension first discovered 4/65, shortly after starting oral contraceptives, headaches frequent. Serum potassium range 2.7 to 3.9 mEq/liter on Enovid. Serum potassium range 3.7 to 3.9 mEq/liter after stop. Metabolism ward study of changes in salt balance revealed striking improvement in renin, aldosterone, and substrate reactivity after terminating contraceptive medication. BP has not been corrected.
			7/20/66 (Off 4 days)	160/110	52	1.4	21	3,505	82	
			7/26/66 (Day 4)	165/115	32	160	12	3,200	80	
			8/1/66 (Day 10)	160/110	32	98	16.8	2,925	94	
			8/22/66	140/110	22	71	3.9	1,430	60	
			8/26/66	140/95	12	193	4.8	970	45	
			8/31/66	120/80	46	3.9	5.8	1,000	50	
			10/11/66	140/80	16	166	4.3	860	29	
			11/15/66	135/108	...	...	...	...	...	
			1/31/67	160/115	...	...	...	...	...	
7	41	Renal hypertension	(Enovid 5 to 10 mg daily for 5 yr)							Chronic renal insufficiency with azotemia. BUN level, 70 mg/100 cc. Hgb level 6.8 gm/100 cc. Hypertension known only last 3 yr, improved after stopping Enovid therapy.
			9/21/66 (Stopped 9/22)	220/120	...	...	4.1	2,795	94	
			12/10/66	140/100	...	...	4.4	1,610	38	
8	32	Essential hypertension	(Enovid 5 mg; 1963 to 2/66)							Hypertension discovered 1/66. Diabetes discovered 2/66. Frequently normotensive in past. Takes 40 units insulin daily. Hypertension appeared during therapy with Enovid; disappeared after its cessation; reappeared with Ortho-Novum; and disappeared again after stopping medication.
			5/25/66	130/80	23	80	4.7	850	27	
			(Ortho-Novum 2 mg; 6/11/66 to 9/21/66)							
			6/23/66	120/80	30	122	12.7	1,980	73	
			9/21/66	200/130	36	101	5.5	4,070	90	
			10/3/66	190/130	19	117	4.8	3,360	60	
			10/26/66	160/110	19	116	6.9	1,400	38	
			1/4/67	130/80	20	225	4.2	980	46	

Data on 11 Women Taking Oral Contraceptives—*Table continued*

Patient	Age	Diagnosis	Regimen, Dates	Blood Pressure (mm Hg)	Aldosterone Excretion (μg/day)	Urinary Sodium Excretion (mEq/day) Rates	Serum Renin Activity (mμg Angiotensin per ml for 4 hr Incubation)	Serum Renin-Substrate (mμg Angiotensin Generated per ml)	Substrate Reactivity (mμg/ml)	Clinical Information
9	36	Essential hypertension	(Oracon; 12/65 to 4/66)							Hypertension discovered 4/66. Repeatedly normotensive prior to this. Five pregnancies without hypertension. Family history strong for hypertension. BP appears improved since second cessation of treatment.
			4/66	220/115	...	...	...	...	...	
			5/13/66	130/80	...	...	...	...	...	
			6/16/66	160/105	19	178	4.8	945	...	
			(Ovulen 1 mg; 8/12/66 to 11/18/66)							
			9/7/66 (Day 17)	170/95	...	...	4.4	3,200	...	
			12/14/66	200/130	...	...	4.9	1,540	43	
			1/18/67	150/90	9.1	66	1.7	...	...	
10	30	Essential hypertension	(Ortho-Novum 2 mg; 1/65 to 11/29/65)							Gained 12 lb during therapy. Severe hypertension, headaches, and dizziness. Hypertension disappeared 3 mo after cessation. Remains normotensive 1 yr later.
			11/29/65	180/140	...	...	...	...	...	
			1/20/66	155/100	8.7	143	3.7	...	...	
11	41	Essential hypertension	(Enovid 10 mg daily; 12/10 to 12/29/66)							Essential hypertension of 23-yr duration which began during pregnancy. Transient rise in BP on day 3 of Enovid. No other significant BP changes during 19-day course. Renin-substrate and substrate reactivity markedly increased by third day of therapy.
			10/20/66	...	22	163	1.7	785	30	
			12/12/66	...	21	142	9.6	2,890	56	
			12/13/66	...	20	41	9.5	3,840	53	
			12/14/66	...	...	52	...	5,135	53	
			12/16/66	...	30	40	7.7	...	62	
			12/19/66	...	33	52	5.8	4,650	56	
			12/29/66	...	26	105	3.3	3,775	52	

*Boldface values are outside the normal range.
†SR=secretion rate.

both, introduction of estrogen-progestogen therapy was associated with early rises in serum renin activity and a subsequent tendency to return to normal levels as maintenance therapy continued. This adjustment of the renin activity levels with sustained administration does not always occur, because in patient 6, serum renin activity remained elevated 15 months after starting treatment. The elevated value in this patient and those in the others promptly returned to normal after administration of the medicine was stopped. In none of the patients studied could the observed increases in serum renin activity be attributed to a state of sodium depletion. In all of the patients studied, the range of urinary sodium excretion together with the absence of clinical edema provide evidence for normal sodium metabolism. In two patients (No. 2 and 6), there was a good correlation between observed increases in serum renin activity and increases in aldosterone excretion. However, in five others, the correlation was not apparent. Patients 4, 5, and 11 exhibited increases in renin not accompanied by simultaneously increased aldosterone excretion. Conversely, patients 1 and 8 tended to exhibit disproportionately higher urinary aldosterone values in the presence of relatively normal renin levels.

Comment

It must be appreciated that both the occurrence of hypertensive disease and the use of oral contraceptives are common phenomena in the female, premenopausal adult population. It is therefore important to recognize that the development or enhancement of hypertensive disease in patients taking these medications might be mere coincidence. However, in the present study a specific cause-and-effect relationship is suggested by sequential clinical observations indicating (1) the onset of hypertension in six of the 11 patients after they started taking the medication, (2) the marked improvement or complete correction of hypertension in six out of eight after they stopped taking the medication, and (3) the reappearance and disappearance (for the second time) of hypertension in two subjects who reinstituted medication.

It is of interest that Swaab,[8] in an abstract to the International Congress of Endocrinology, stated that he had observed cases in which blood pressure rose markedly during the use of oral contraceptives. However, to our knowledge, no data have yet been published.

The administration of pharmacological doses of estrogen and progestogen required for contraceptive action was found to produce a number of abnormalities in the renin-angiotensin-aldosterone system, some of which have been previously recognized. Thus, other investigators have also observed significant increases in aldosterone secretion and excretion following administration of Enovid,[9] and

this effect appeared to be largely due to the presence of the progestogen, norethynodrel, in the preparation.[9,10] It has also been shown that the administration of Enovid can produce significant increases in a plasma aldosterone-binding protein, an effect which seemed to be due to the estrogenic component of the medication.[11]

The most impressive and consistent abnormality observed in the present study was the striking increase in the concentration of serum renin-substrate. This observation confirms the original report of Helmer and Griffith[12] which demonstrated a marked increase in renin-substrate in rats given diethylstibestrol. Helmer and Griffith also found that the effect did not occur with progesterone, could be neutralized by the administration of androgen, and was not modified by removal of the pituitary or adrenal glands.

In every instance studied, it was possible to demonstrate that the observed increase in renin-substrate concentration was associated with a marked enhancement in the rate of angiotensin formation upon addition of a fixed amount of endogenous renin to the serum. These observed increases in reactivity to renin suggest that increases in the concentration of substrate above normal can exert an important accelerating influence on the rate of production of angiotensin. The finding is somewhat surprising since it has been thought that substrate is normally present in amounts which are sufficient to provide nearly maximum enzyme elocity.[4,13] The possibility of a qualitative alteration in the substrate molecule or of a role for an activator or inhibitor of the renin-substrate reaction remains to be investigated. Despite the presence of increased substrate and increased substrate reactivity, persistent increases in net endogenous renin "activity" were only observed in about half of the patients. These data indicate that the true renin concentration, when corrected for the augmenting effect of the increased substrate, must at times have been actually reduced as a consequence of oral contraceptive administration. Recently, Crane et al[14] have reported increases in plasma renin activity in seven normal subjects who were given doses of ethinyl estradiol. The dosage employed was much larger than that contained in oral contraceptive medications. An effect on renin-substrate levels was not considered, although this may have been a major factor in the observed increases.

The relevance of these observed biochemical abnormalities to the production or augmentation of hypertension remains obscure because we have repeatedly observed the same abnormalities in patients exhibiting no change whatever in their blood pressure. One can only speculate about the possibility that in certain susceptible individuals the induced increases in substrate concentration lead to an increased reactivity towards endogenous renin which cannot be adequately compensated for by appropriate adjustments in the complex homeostatic systems which normally operate to regulate blood pressure and salt balance.

Because the renin-substrate is made in the liver,[15] and because estrogens appear to increase[11] or decrease[16] the synthesis of various other proteins, it seems possible that the estrogens raise the serum renin-substrate by stimulating hepatic biosynthesis. An alternate possibility would be an effect of estrogens on the kidney, since renal insufficiency and nephrectomy often produce sharp rises in renin-substrate concentration.

The possible relevance of the effect of steroids with estrogenic and progestogenic activity on the pathogenesis of hypertensive disease, and especially on the hypertensive states occurring during pregnancy, will require much more study. This preliminary report is submitted to alert clinicians to a possible relationship.

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Generic and Trade Names of Drugs

Norethindrone with mestranol—*Ortho-Novum, Norinyl, Norinyl-1.*
Norethynodrel with mestranol—*Enovid, Enovid E.*
Dimethisterone with ethinyl estradiol—*Oracon.*
Ethynodiol diacetate with mestranol—*Ovulen, Metrulen.*

References

1. Laragh, J.H.; Sealey, J.E.; and Sommers, S.C.: Patterns of Adrenal Secretion and Urinary Excretion of Aldosterone and Plasma Renin Activity in Normal and Hypertensive Subjects, *Circ Res* **28 & 29** (suppl 1): 158-174 (June) 1966.

2. Fleming, R.J., et al: Hypertension and Unilateral Renal Disease: The Usefulness of Modified Intravenous Urography, *Circulation* **32**:682-685 (Nov) 1965.

3. Laragh, J.H.; Sealey, J.E.; and Klein, P.D.: The Presence and Effect of Isotope Fractionation in Isotope Dilution Analysis: A Factor in the Measurement of Aldosterone Secretory Rates in Man in Radiochemical Methods of Analysis, Vienna: International Atomic Energy Agency, 1965, vol 2, pp 353-370.

4. Pickens, P.T., et al: Measurement of Renin Activity in Human Plasma, *Circ Res* **17**:438-448 (Nov) 1965.

5. Sealey, J.E., et al: The Inhibition of Renin by Heparin, *J Clin Endocr* **27**:699-705 (May) 1967.

6. Haas, E.; Goldblatt, H.; and Gipson, E.C.: Extraction, Purification and Acetylation of Human Renin and the Production of Anti-Renin to Human Renin, *Arch Biochem* **110**:534-543 (June) 1965.

7. Ledingham, J.G.G.; Bull, M.B.; and Laragh, J.H.: The Meaning of Aldosteronism in Hypertensive Disease, *Circ Res* **21** (suppl 2): 177-198 (July) 1967.

8. Swaab, L.I.: "Blood Pressure and Oral Contraception" in *Proceedings of Second International Congress on Hormonal Steroids, Milan, Italy,* Amsterdam: Excerpta Medica Foundation, 1966, p 198.

9. Layne, D.S., et al: The Secretion and Metabolism of Cortisol and Aldosterone in Normal and in Steroid-Treated Women, *J Clin Endocr* **22**:107-118 (Feb) 1962.

10. Laidlaw, J.C.; Ruse, J.L.; and Gornall, A.G.: The Influence of Estrogen and Progesterone on Aldosterone Excertion, *J Clin Endocr* **22**:161-171 (Feb) 1962.

11. Meyer, C.J., et al: The Binding of Aldosterone to Plasma Proteins in Normal, Pregnant and Steroid-Treated Women, *J Clin Invest* **40**:1663-1671 (Sept) 1961.

12. Helmer, O.M., and Griffith, R.S.: The Effect of the Administration of Estrogens on the Renin-Substrate (Hypertensinogen) Content of Rat Plasma, *Endocrinology* **51**:421-426 (Nov) 1952.

13. Haas, E.; and Goldblatt, H.: Kinetic Constants of the Human Renin and Human Angiotensinogen Reaction, *Circ Res* **20**:45-55 (Jan) 1967.

14. Crane, M.G.; et al: Effect of Ethinyl Estradiol (Estinyl) on Plasma Renin Activity, *J Clin Endocr* **26**:1403-1406 (Dec) 1966.

15. Braun-Menendez, E., et al: *Renal Hypertension,* Springfield, Ill: Charles C Thomas, Publisher, 1946, pp 130-132.

16. Robertson, G.S.: Serum Protein and Cholinesterace Changes in Association With Contraceptive Pills, *Lancet* **1**:232-235 (Feb 4) 1967.

HIGH BLOOD PRESSURE AND ORAL CONTRACEPTIVES

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High blood pressure and oral contraceptives

Changes in plasma renin and renin substrate and in aldosterone excretion

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A group of patients is described in whom the development or augmentation of hypertensive disease was associated with use of oral contraceptives. The experience suggests a causal role for these hormonal substances in certain susceptible individuals. Factors which might sensitize to the pressor effect of these drugs remain undefined. However, the effect may be related to marked associated changes observed in certain components of the renin-angiotensin-aldosterone hormonal interaction. The contraceptive medications consistently produced large sustained increases in plasma concentration of renin substrate. Less consistently, transient or sustained increases in plasma renin and in aldosterone were also observed. Parallel in vitro studies demonstrated that renin substrate is normally not present in excess because the contraceptive-induced increased substrate concentration was always accompanied by a significantly increased capacity for angiotensin formation when renin was added to the plasma. It seems possible that, in certain susceptible subjects, these induced hormonal changes, together with associated changes in sodium metabolism, could compromise the buffer capacity of the renin-angiotensin-aldosterone hormonal system, permitting exaggerated (pressor) responses to circulating renin when it is released by the normal physiologic stimuli. These observations also may be relevant to the use of female hormones in other clinical situations, and they may be applicable to the study of hypertension in experimental models.

IN THIS communication we present studies stimulated by clinical observations in certain of our hypertensive patients which first suggested the possibility of a cause-and-effect relationship between the use of oral contraceptives and either the development or enhancement of high blood pressure.

At the outset it should be emphasized that because of the widespread use of these medications it seems very likely that in the large majority of those who take them they do not induce hypertension. However, observations that we have made in 11 selected hypertensive patients suggest that in special circumstances these hormonal agents may become critically involved in the production of hypertensive disease. A preliminary report of these findings has been published.[1]

When clinical observations first suggested this relationship, it was decided to investigate concurrently the effects of these female hormonal substances on electrolyte metabolism and on the behavior of the renin-angiotensin-aldosterone hormonal interaction. This seemed appropriate because of the known relationship of this hormonal system to other forms of hypertensive disease and because previous work (Table I) had indicated that estrogens and progestogens can significantly

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affect various components of this renal-adrenal hormonal system.[1-9]

Methods and material

Eleven women with high blood pressure have been studied. Using previously defined criteria,[10] we classified 8 as having uncomplicated benign "essential" hypertension, 2 as renal hypertension, and one as advanced hypertension. Most of the patients were observed in the outpatient department, but 3 were admitted to the metabolism ward and studied under conditions of controlled electrolyte balance. In addition, the effects of oral contraceptives were evaluated further in metabolism ward studies of 2 fully informed normal male volunteers and in another male subject with uncomplicated essential hypertension.

Aldosterone secretion and excretion rates were measured by a double isotope dilution technique previously described.[10, 11] Blood samples for estimation of renin were taken at noon, when the patients had been ambulatory for about 4 hours. Renin activity, renin substrate concentration, and the rate of angiotensin formation in response to a fixed amount of exogenous renin were all measured by a modification of the method of Pickens and associates.[12] In our modification each incubation is carried out for 16 and for 24 hours in isotonic salt in the presence of EDTA and DFP. For studies designed to evaluate the capacity for angiotensin formation in a given plasma, a fixed amount of exogenous renin was added to the sample. In the earlier studies a final concentration of 0.0034 Goldblatt unit per milliliter of renin was employed in a 4 hour aqueous incubation.[1] In more recent studies (Fig. 6), 0.0017 Goldblatt unit per milliliter was employed with a one hour incubation in saline. Highly purified angiotensinase-free renin was prepared from human kidneys according to the method of Haas, Goldblatt, and Gipson.[13]

Table I. Oral contraceptives, hypertension, and abnormalities in the renin-angiotensin-aldosterone hormonal interaction

Elevated levels	*Agent*	*Authors*
1. Plasma angiotensinogen	Estrogen	Helmer and Griffith,[2] 1952
2. Aldosterone secretion	Progestogen, estrogen	Layne and associates,[3] 1962
3. Plasma renin	Pregnancy	Brown and associates,[5] 1963 Winer,[6] 1965 Genest and associates,[7] 1965
4. Plasma renin	Estrogen (large doses)	Crane and associates,[8] 1966
5. Blood pressure	Oral contraceptives	Laragh and associates,[1] 1967 Woods,[9] 1967
6. Plasma reactivity to renin	Oral contraceptives	Laragh and associates,[1] 1967

Results

A summary of our previously reported observations[1] associating oral contraceptive therapy with changes in arterial blood pressure and with changes in the renin-angiotensin-aldosterone system is presented in Table II.

Effects on arterial blood pressure (Table II). Because of the frequent use of oral contraceptives and the high incidence of hypertensive disease in the population at large, the fact that hypertensive disease was first discovered in 6 of our patients receiving this treatment does not in itself imply any specific interrelationship. Furthermore, even the augmentation of pre-existing hypertension observed in 2 of 5 previously hypertensive patients could be a chance occurrence.

Table II. Oral contraceptives and high blood pressure*

1. 6 normotensive prior to medication
2. 5 hypertension known prior to medication
   - 2, hypertension augmented
   - 3, hypertension unchanged
3. 9 medication withdrawn
   - 3, normalized blood pressure
   - 3, improved
   - 3, unchanged
4. Reappearance of hypertension with restoration of treatment in each of two
5. Marked consistent elevation of angiotensinogen with increased plasma reactivity to renin
6. Less consistent or persistent increases in plasma renin levels and aldosterone secretion

*Findings in 11 patients presenting with hypertension.

However, the complete reversal of documented hypertension after drug withdrawal in 3 of 9 and the improvement of hypertension in another 3 of the 9 raise the possibility of a more specific relationship. In Fig. 1 the time course for blood pressure improvement and for correction of associated abnormalities in the renin-angiotensin system is presented for 4 of these patients.

In 2 patients, in each of whom correction or considerable improvement in blood pressure was observed after drug withdrawal, the oral contraceptives were readministered. In both, hypertension returned and, concurrently, characteristic abnormalities in the renin-angiotensin-aldosterone system reappeared. Such sequential observations (Fig. 2), demonstrating reappearance and redisappearance of hypertension, perhaps provide the most convincing evidence, suggesting a specific connection between the administration of oral estrogen-progestogen and the development of high blood pressure.

One patient (Table II) who had hypertension prior to the use of contraceptives also seems to have been cured of the condition by drug withdrawal.[1] She first developed hypertension during pregnancy and subsequently underwent nephrectomy for unilateral renal infection. Pre-existing hypertension in the region of 180/110 persisted during 20 months of oral contraceptive therapy. However, she has now been normotensive for over a year since stopping medication.

Effects on renin substrate. The most consistent attendant biochemical abnormality was the appearance of marked and persistent increases in the concentration of plasma angiotensinogen, observed in all but one of the hypertensive women studied (Figs. 1 to 4). The elevated values ranged from 1,980 to 8,650 ng. of angiotensin generated per milliliter of plasma or to as much as eightfold the normal concentration. In 2 normal male subjects and in one male hypertensive patient (Figs. 5 and 6), entirely similar changes were produced by treatment with these agents.

The maximum effect on renin substrate with the use of a combined estrogen-progestogen was observed to develop from as soon as 4 days to as long as 2 weeks after starting

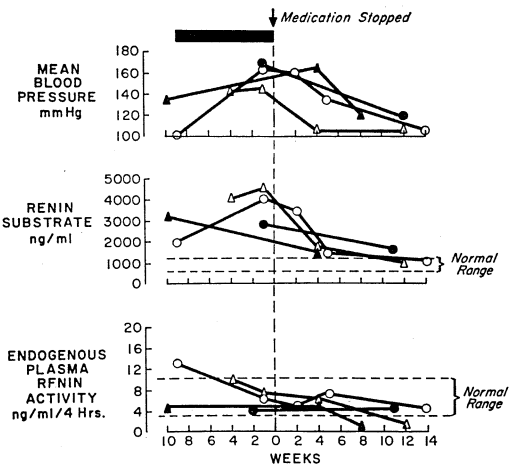

Fig. 1. Effects of withdrawal of oral contraceptives in 4 patients. After withdrawal of medication elevated blood pressure was improved in 2 and completely corrected in 2 others. At the same time elevated renin substrate levels returned to normal and plasma renin levels, though not abnormal, tended to decline. It is of note that plasma renin levels were at times elevated earlier in treatment but tended to decline as therapy was continued.

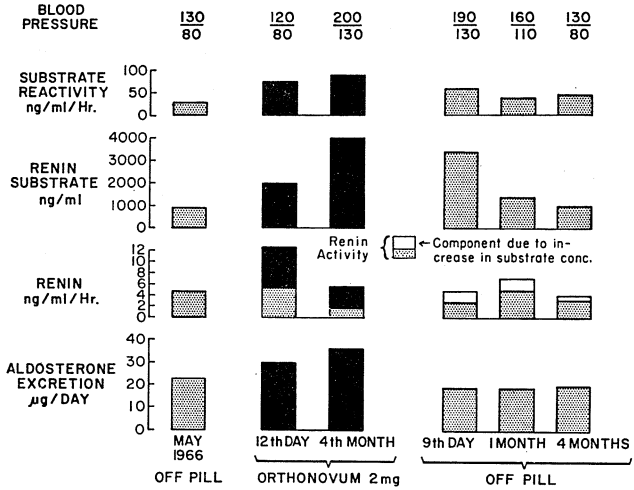

Fig. 2. Oral contraceptive hypertension in a 32-year-old woman in whom hypertension was first discovered after 3 years of oral contraceptive therapy with Enovid 5 mg. Hypertension disappeared after drug withdrawal. It reappeared, as shown here, when treatment was renewed, and then disappeared again after drug withdrawal. The onset and offset of hypertension was associated with concomitant increases and decreases in renin, aldosterone, renin substrate and reactivity to renin. The data illustrate that in this patient the observed increase in renin activity was largely due to an increase in renin substrate concentration.

treatment (Figs. 2 and 3). The time required for return of substrate levels to the normal range after drug withdrawal exhibited even more variation. Two to 4 weeks' time or even longer was often required for the return of substrate levels to a normal range (Fig. 1).

An attempt was made to determine which component of an oral contraceptive preparation was responsible for this biochemical effect (Fig. 5). The administration of norethynodrel produced significant, but smaller, increases in renin substrate than that observed with the use of either ethinyl estradiol or the combination pill. These results in 2 male subjects suggest that both components of the oral contraceptives can stimulate substrate formation with the predominant effect being referable to the estrogen. The stimulating effect of norethynodrel may derive from its estrogenic properties, since progesterone was found not to increase renin substrate in a previous report.[2]

Effects on the plasma reactivity to exogenous renin (Figs. 2 to 6). Because of the striking increases observed in renin substrate levels, a study was made to determine whether this abnormality might produce a change in the character or magnitude of the response to renin. This question was approached with an in vitro system in which the capacity to form angiotensin was measured after the addition of a fixed amount of renin to the individual plasma.

Significant increases in substrate reactivity were consistently observed. These increases were directly related to the corresponding induced rise in renin substrate concentration. Increased reactivity was produced as the substrate concentration increased to the region of 2,000 ng. per milliliter. Above this concentration further increases in substrate induced lesser increments in reactivity. In the one patient in whom substrate failed to increase significantly, no increase in reactivity to renin was produced.[1] These results suggest

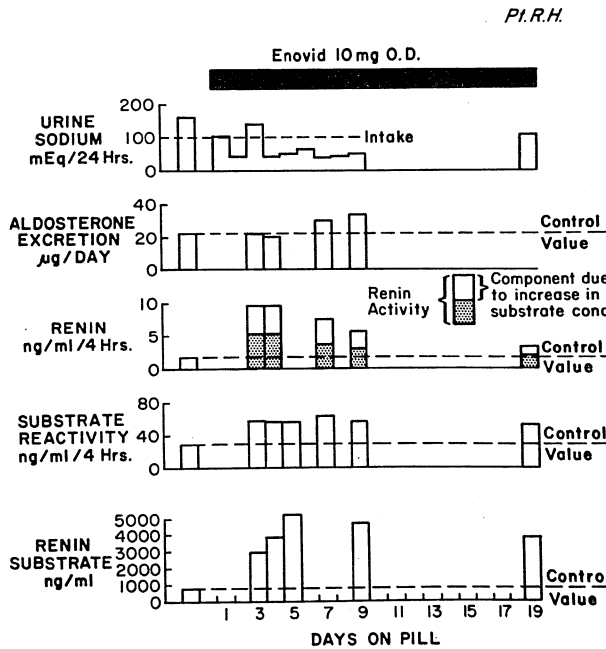

Fig. 3. Effects of administration of an oral contraceptive administered for 19 days to a 41-year-old woman with essential hypertension. In this patient the drug produced a slightly positive sodium balance. At the same time aldosterone excretion exhibited a significant rise which seemed slightly out of phase with the increased renin. The prompt rise in plasma renin activity appeared to be due to both an increase in endogenous renin and to an increased reactivity from increased substrate concentration. With continued treatment elevated renin activity tended to fall back to the normal range even though the increased renin substrate persisted.

that it is the change in concentration of substrate which accounts for the increased reactivity. Other in vitro studies in which reactivity was measured after addition of estrogen to normal plasma indicated that the presence of the estrogen does not per se modify the rate of reaction between renin and its substrate.

Previous studies have suggested that under normal conditions substrate concentration is not rate limiting so that the reaction velocity for a given amount of renin is near maximum.[12, 14, 15] Because of these reports the possibility may be raised that the consistent increases in reactivity to renin produced by the contraceptives might alternatively have resulted from modification of the plasma concentration of an activator or an inhibitor. To test this possibility, a plasma sample with a substrate concentration of 3,000 ng. per milliliter angiotensinogen, drawn at the time of maximum effect on substrate concentration, was diluted, and the reactivity of various dilutions of this sample was compared with that of other samples drawn from the same patient as the substrate concentration was rising (Fig. 6). The two curves of reactivity as related to substrate concentration were superimposable. This result provides no positive evidence for any activator or

inhibitor and instead suggests that the increased reactivity to renin merely results from an increased substrate concentration.

Effects on endogenous plasma renin activity. Because of the consistently produced enhancement of plasma reactivity to renin, proper evaluation of the influence of oral contraceptive therapy on the true renin concentration requires that each measurement of endogenous renin activity be corrected by taking into account and correcting for the contribution of these alterations in reactivity (Figs. 1 to 5). Such data indicate that the observed apparent increases in endogenous renin activity resulted from either an increase in plasma reactivity or an increase in the true renin concentration or both (Fig. 3).

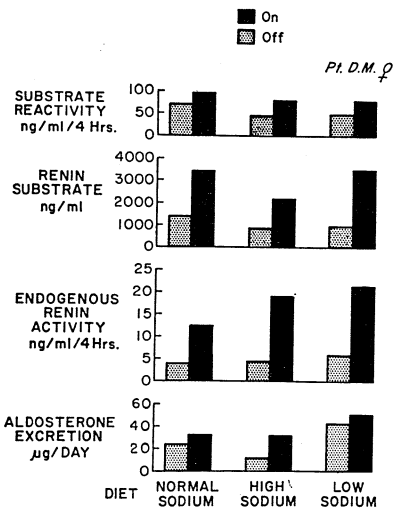

Fig. 4. The influence of changes in dietary salt intake on oral contraceptive induced abnormalities in the renin-angiotensin-aldosterone system. Data taken from a metabolism balance study of a 30-year-old woman who had been maintained on Enovid 2.5 mg. for 17 months and whose hypertension in the region of 160/110 was discovered shortly after starting the treatment. This patient exhibited persistent and significant increases in all of the measured components of the renin-angiotensin system. The abnormalities were apparent at all levels of sodium intake. The fluctuations of plasma renin levels with various regimens did not appear altogether appropriate.

With long-term administration of oral contraceptives, endogenous renin activity remained elevated in 4 patients, but in 5 others the values were normal.[1] Normalization of the endogenous renin activity levels in this situation suggests that true renin concentration actually may have been depressed below normal, with activity values being normal because of the raised substrate.

An example of a patient with persistently increased plasma renin levels is presented in Fig. 4. The data illustrate that the abnormality persists at all levels of sodium intake. The second pattern, i.e., the tendency for endogenous renin activity to return to normal after an initial rise, is illustrated by studies of 2 other hypertensive patients (Figs. 2 and 3) and of 2 normotensive males (Fig. 5).

Effects on aldosterone secretion or excretion. Abnormalities in aldosterone tended to be transient, and they were observed less consistently. In 4 of 8 hypertensive patients studied the levels remained elevated. However, in one the increase seemed referable to severe pre-existing hypertensive disease. In the other 3 (Figs. 2 to 4), the values were restored to normal by cessation of therapy. In 2 normal male subjects only transient increases in aldosterone excretion were induced in association with the transiently increased endogenous renin activity.

Comment

Because both hypertensive disease and the use of oral contraceptives are such common phenomena in the adult female premenopausal population, the development or enhancement of hypertension in subjects taking this medication could be mere coincidence. Notwithstanding this, in the present study considerable evidence has been advanced which suggests a cause-and-effect relationship between the use of this type of medication and the development or aggravation of high blood pressure in certain individuals who seem especially sensitive in this regard. Furthermore, these clinical observations are

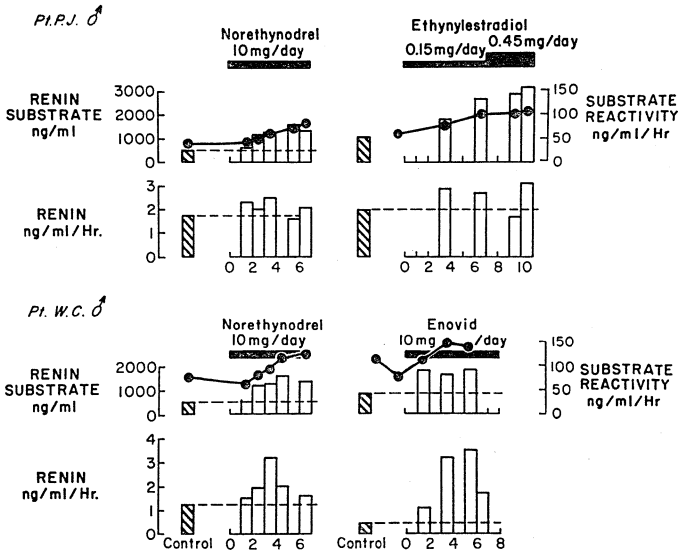

Fig. 5. Relative effects of progestogen and estrogen (norethynodrel, Enovid, or ethinyl estradiol) on renin, renin substrate, and plasma reactivity to renin. Studies made in 2 normal male volunteers receiving a constant regimen. In both subjects renin substrate and plasma reactivity to renin were increased to a greater extent by either estrogen or an estrogen combination. The progestogen exhibited similar but smaller effects.

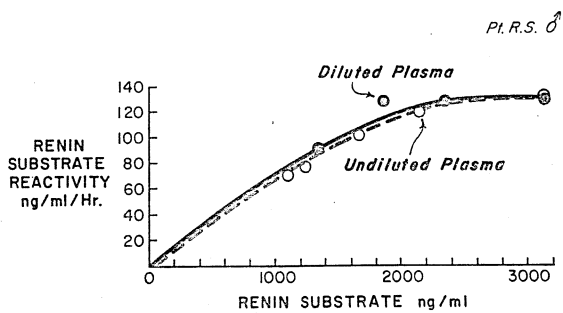

Fig. 6. Effect of dilution of renin substrate on substrate reactivity compared with undiluted samples exhibiting various concentrations. These samples were obtained at other times in the course of oral contraceptive administration. The data strongly suggest that observed changes in the substrate capacity to release angiotensin are directly related to changes in the substrate concentration rather than the result of variation in concentration of an activator or inhibitor.

now supported by findings from other clinics.[9, 16, 17]

The most impressive and consistent abnormality observed in the present investigation was the striking increase in the concentration of plasma angiotensinogen. In every instance it was possible to demonstrate that this observed increase in renin substrate concentration was associated with a marked enhancement in the rate of angiotensin formation upon addition of a fixed amount of endogenous renin to the plasma. These increased responses suggest that increases in the concentration of substrate above normal levels can exert an important accelerating influence on the rate of production of angiotensin, so that the rate of angiotensin formation can be increased by as much as the factor of two. The finding is somewhat surprising, since it has previously been thought that substrate is normally present in amounts which are sufficient to provide nearly maximum enzyme velocity.[12, 14, 15] However, while the findings in this study demonstrate that normal concentrations of renin substrate are insufficient to produce a maximum rate of reaction with renin, they also suggest that, from a physiologic standpoint, the suboptimum substrate concentrations of normal subjects are probably not rate limiting for angiotensin production. This is strongly suggested by the observation that when substrate concentrations are elevated by this drug, there is often a tendency for the renin concentration to fall so that the rate of formation of angiotensin tends to remain unchanged. Thus, there is a tendency to autoregulate the formation of the final product, angiotensin.

In addition to their effects on substrate concentration, these hormonal substances appear to act by another means to produce true increases in levels of plasma renin. Thus, in some patients increased endogenous plasma renin activity could be accounted for by increases in the plasma angiotensinogen concentration. However, in others, either transient or sustained increases in renin activity were of greater magnitude than could be accounted for by the aforementioned mechanism. It therefore seems likely that these female hormonal substances can act by other, possibly more direct, means to increase plasma renin concentration. It is clear that the increases in plasma renin were not consequent to induced sodium depletion, since oral contraceptives or their components generally tend to promote fluid retention.

The relevance of the observed derangements in the renin-angiotensin-aldosterone system to the associated production or augmentation of hypertensive disease remains obscure. This is because we have repeatedly observed the same abnormalities in patients receiving the same medications, who at the same time exhibited no change whatever in their blood pressure. However, one may speculate about the possibility that in certain susceptible individuals the induced increased reactivity toward endogenous renin may reduce the buffer capacity of this hormonal interaction. In this way the increased responsiveness to renin, perhaps aided by the second direct stimulating effect on renin secretion, might create a situation leading to an exaggerated pressor response to the usual physiologic stimuli for renin release. This idea that, in certain subjects, feedback compensation for the angiotensinogenemia produced by these drugs may be incomplete, is perhaps supported by our observations illustrating that only some patients fully compenated for the induced increases in renin substrate levels by suppressing their renin secretion.

One can only speculate about the factors which might act to sensitize certain individuals to the pressor action of these contraceptive agents. Pre-existing occult renal disease with reduced buffer capacity of the renin angiotensin system may be one factor as evidenced in 2 such patients included in our series and in one other now under study. Another sensitizing factor may be related to the tendency for sodium and water retention produced by these drugs in certain individuals. In future studies serial measurements of sodium balance or of sodium spaces or weight fluctuations[18] in outpatients may be especially illuminating. The oft repeated pro-

posal[3] that the aldosteronism of progestational compounds is secondary to a natriuresis seems quite unlikely in these patients, often exhibiting a weight gain on these drugs.

Renin substrate is made by the liver.[19] Estrogens appear to increase or decrease the synthesis of various other proteins,[1] including a cortisol-binding globulin and an aldosterone-binding protein.[20] It therefore seems possible that the estrogens raise the serum renin substrate by stimulating hepatic biosynthesis. Renin substrate levels may be sharply reduced in patients with cirrhosis.[21] However, in one such patient, we produced a striking rise in angiotensinogen with oral contraceptives, possibly indicating a potentially adequate hepatic biosynthetic capacity. An alternate possibility to explain the angiotensinogenemia would be an effect of estrogens and progestogens on the kidney, since renal insufficiency and nephrectomy often produce sharp rises in renin substrate concentration.

Full understanding of the role of estrogenic and progestogenic steroids in the pathogenesis of various forms of hypertensive disease, especially the forms observed during pregnancy, will require further study. The observations reported here may be applicable to the study of hypertension in experimental models. Furthermore, they may be relevant to the use of female hormones in other clinical situations. Of note in this regard are the reports of strokes in young women using oral contraceptives[22] and of a significant incidence of cerebrovascular accidents in a large group of males[23] receiving estrogen treatment for prostatic carcinoma.

REFERENCES

1. Laragh, J. H., Sealey, J. E., Ledingham, J. G. G., and Newton, M. A.: J. A. M. A. **201:** 918, 1967.
2. Helmer, O. M., and Griffith, R. S.: Endocrinology **51:** 421, 1952.
3. Layne, D. S., Meyer, C. J., Vaishwanar, P. S., and Pincus, G.: J. Clin. Endocrinol. **22:** 107, 1962.
4. Laidlaw, J. C., Ruse, J. L., and Gornall, A. G.: J. Clin. Endocrinol. **22:** 161, 1962.
5. Brown, J. J., Davies, D. L., Doak, P. B., Lever, A. F., and Robertson, J. I. S.: Lancet **2:** 900, 1963.
6. Winer, B. M.: J. Clin. Invest. **44:** 112, 1965.
7. Genest, J., de Champlain, J., Veyrat, R., Boucher, R., Tremblay, G. Y., Strong, C. G., Koiw, E., and Marc-Aurèle, J.: Proc. Council High Blood Pressure Res. **13:** 97, 1964.
8. Crane, M. G., Heitsch, J., Harris, J., and Johns, V. J., Jr.: J. Clin. Endocrinol. **26:** 1403, 1966.
9. Woods, J. W.: Lancet **2:** 653, 1967.
10. Laragh, J. H., Sealey, J. E., and Sommers, S. C.: Circulation Res. (Suppl. 1) **19:** 1, 1966.
11. Laragh, J. H., Sealey, J. E., and Klein, P. D.: *In* Radiochemical Methods of Analysis, Vienna, 1965, International Atomic Energy Agency, vol. II, p. 353.
12. Pickens, P. T., Bumpus, F. M., Lloyd, A. M., Smeby, R. R., and Page, I. H.: Circulation Res. **17:** 438, 1965.
13. Haas, E., Goldblatt, H., and Gipson, E. C.: Arch. Biochem. **110:** 438, 1965.
14. Haas, E., and Goldblatt, H.: Circulation Res. **20:** 45, 1967.
15. Skinner, S. L.: Circulation Res. **20:** 391, 1967.
16. Swaab, L. I.: *In* Proceedings of Second International Congress on Hormonal Steroids, Milan Italy, Amsterdam, 1966, Excerpta Medica Foundation, p. 198.
17. Shapiro, A. P.: Personal communication.
18. Thomas, C. B.: Ann. Int. Med. **39:** 289, 1953.
19. Braun-Menendez, E., Fasciola, J. C., Leloir, L. F., Munoz, J. M., and Taquini, A. C.: Renal Hypertension, Springfield, Illinois, 1946, Charles C Thomas, Publisher, p. 130.
20. Meyer, C. J., Layne, D. S., Tait, J. F., and Pincus, G.: J. Clin. Invest. **40:** 1663, 1961.
21. Ayers, C. R.: Circulation Res. **20:** 594, 1967.
22. Cole, M.: Arch. Int. Med. **120:** 551, 1967.
23. The Veterans Administration Cooperative Urological Research Group: Surg. Gynec. & Obst. **124:** 1011, 1967.

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Senator DOLE. The hearings will resume tomorrow morning at 9:30.

(Whereupon, at 11:30 a.m., the subcommittee adjourned, to reconvene at 9:30 a.m., Thursday, January 22, 1970.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

THURSDAY, JANUARY 22, 1970

U.S. SENATE,
SUBCOMMITTEE ON MONOPOLY,
OF THE SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 9:35 a.m., in room 2221, New Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson, McIntyre, and Dole.

Also present: Benjamin Gordon, staff economist; Elaine C. Dye, clerical assistant; and James P. Duffy III, minority counsel.

Senator NELSON. Come to order, please.

Our first witness this morning is Dr. Louis Hellman. Professor Hellman is professor and chairman of the Department of Obstetrics and Gynecology of the State University of New York. Dr. Hellman has served as Chairman of the Advisory Committee on Obstetrics and Gynecology of the Food and Drug Administration.

Dr. Hellman, we are very pleased to have you come here to testify today. We appreciate your taking the time to do so. I realize it is an imposition on everybody's busy schedule.

You may present your statement in any way you desire. If you wish to extemporize from it at any time or elaborate on anything you have said, feel free to do so. Your statement will be printed in full in the record.

I assume that if any members have questions, you do not mind being interrupted in the course of your testimony.

STATEMENT OF DR. LOUIS M. HELLMAN, PROFESSOR AND CHAIRMAN, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, STATE UNIVERSITY OF NEW YORK, DOWNSTATE MEDICAL CENTER, BROOKLYN, N.Y.

Dr. HELLMAN. Delighted, sir.

Senator NELSON. If you will, pull the microphone toward you and speak directly into it so you may be heard.

Dr. HELLMAN. Please let me know if I cannot be heard.

Senator Nelson and members of the subcommittee, it is a pleasure to appear before your subcommittee to discuss the oral contraceptives. As Senator Nelson said, I am at present professor and chairman of

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the Department of Obstetrics and Gynecology of the State University of New York, Downstate Medical Center, and I am director of the largest maternity service in the city of New York and also one of the largest contraceptive family planning clinics in the city. This clinic treats 4,000 new patients a year and has on its rolls 22,000 patients. All of them are from ghetto population. I have a very small private practice.

From the middle of November 1965 until December of this year, I served as Chairman of the Advisory Committee on Obstetrics and Gynecology of the Food and Drug Administration. At present, I am Deputy Assistant Secretary for Population Affairs, Designate, of the Department of Health, Education, and Welfare.

Senator Nelson, I will take you at your word and deviate a little bit from my prepared statement from time to time. I would like to cover a bit of the history of development of modern contraceptive practices, and also a bit of the history of governmental, and regulatory and scientific concern over the modern contraceptives.

We have three types of contraception available to the world's population today. I suppose the first type can really be classified as folklore. This includes coitus interruptus—withdrawal—and the belief that prolonged lactation limits family growth. I do not think we need to talk very much about either one of them. Neither method has been popular in the United States.

We then have the traditional methods of contraception. These include the diaphragm, the condom, the foams, and the jellies. They date back many years and were all that were available to us up until 1960.

Roughly in about 1960, the new or modern methods of contraception were introduced and they made about as much difference to contraception as the jet airplane made to methods of travel. They were different in several ways. We have two modern methods, the intrauterine device, which is a mechanical method, and the oral contraceptives, which are hormonal methods. They are different from the traditional methods in that they are not related to coitus. They could be taken at a time far removed from the sexual act. They were different in the magnitude of their effectiveness. They were usable by populations that neither had the privacy nor the motivation to use the traditional methods.

Both, interestingly enough, were introduced about 1960, and both have become fairly popular, although the oral contraceptives use far exceeds that of the intrauterine devices.

Now, governmental concern and scientific concern about these methods began in about 1961 or 1962 when we began to have reports of difficulty with the oral contraceptives in respect to vascular or clotting diseases. By 1963, these reports, which were scattered case reports at first, had become so serious that governments took cognizance of them. The Food and Drug Administration in this country appointed an ad hoc committee under the chairmanship of Irving Wright to look into thromboembolism, and in England the Committee on the Safety of Drugs, headed by Sir Derrick Dunlap, also undertook the same task.

In addition to that, 2 years later, in 1965, the World Health Organization felt that this problem merited consideration. There had also been scientific meetings.

In essence, the reports of these three agencies in 1965 were virtually the same. Based on case reports they recognized that there might be trouble, but when they looked into the scientific base for information, they were unable to get sufficient data on the subject to come to any conclusion. The reasons for this are several: One, the base data; the incidence or prevalence of thromboembolic disease in the population was not known with accuracy, either in Great Britain or in the United States.

Second, the method of reporting or methods of reporting adverse reaction to drugs, both in Britain and the United States, were not very good, not very sophisticated, and they are still not very good.

In 1965, the Commissioner of the U.S. Food and Drug Administration decided that this problem was of sufficient seriousness so that an ad hoc committee was appointed, of which I was chairman, to look into the problem of the modern contraceptives with specific emphasis on the oral contraceptive. I had nothing to do with the choosing of the members of the committee, but, if I had, I could not have chosen better. In the first place, and importantly, there were some female members of the committee. Women use these drugs and it is important that they be presented in any decisionmaking body. Among the committee members were obstetricians and gynecologists of prominence, endocrinologists, and epidemiologists.

The committee was hard working and it worked continually against deadlines. Its first meeting was held in November of 1965 and it was told in the spring of 1966 by the new Commissioner, Dr. James Goddard, that the deadline for the first report was the 1st of August 1966. We met that deadline, and I think the first report is in your hands, Senator. If it is not, we certainly can make it available to you.

This report reflected the same general lack of basic knowledge that confronted the previous committee. Particularly there was no knowledge, no fundamental knowledge, on the thromboembolic disease. There was suspicion about malignancy. Compared to what we know today, there was very little known about the metabolic changes.

The Committee made 10 recommendations and a conclusion. Its recommendations were acted on quite promptly by the Food and Drug Administration, and the Public Health Service, with the exception of one recommendation, namely, that a large population be obtained that could be followed carefully. We made many attempts to find such a population that took the oral contraceptives over a long period of time that was susceptible to medical followup. We tried what you all might think was a good lead, the armed services, only to find that the data from the armed services and the movement of people in and out of the armed services made this source of information not very secure.

Our only large study, with long-term followup that merits consideration was the followup study of the Kaiser Permanente group, a captive population that can be looked at over time. One of the serious problems in this whole investigation is to get a population that you can observe over a long period of time.

The Committee made trips to each of the seven pharmaceutical houses that made oral contraceptives at that time to investigate reporting of adverse reactions. The committee actually appointed a consultant, Dr. Kohl, who happened to work in my department, to make these visits. I made one with him. I must say the pharmaceutical in-

dustry was more than cooperative. The files were opened to us. We looked at adverse reaction reporting about as well as anybody could in the short period of time available to us.

Adverse reaction reporting has a lot of pitfalls. In the first place, at that time, there was no uniform reporting sheet from the drug houses. This has been corrected. The method of data retrieval in FDA was deficient. You could not get quickly the information that you needed. Some of it was computerized, some of it was not. There have been efforts in FDA to correct this. I think the system still needs a good, hard look and some correction if correction is possible.

The chief difficulty with adverse reaction reporting, both in the United States and Great Britain, comes from the reluctance of the physicians themselves to report to anybody an adverse reaction. In this country it is easy to understand, because the physician does, to a certain extent, incur some liability, legal liability, in reporting an adverse reaction to anybody, and he is often very hesistant to do this.

Second, it is very difficult for a physician to tell whether what he actually sees in the patient is related to some even like taking the oral contraceptive or something entirely different. In Great Britain, where you have a National Health Service, the reporting of adverse reactions is a little better. But I do think that because we now use many, many powerful drugs that were unknown 20 years ago, and many of them have adverse reactions which, even with the most careful testing, we might not detect, that it is very important that we in the United States and people in Great Britain, and perhaps from other countries of the world, hold some kind of an international meeting to discuss the problems of how we are going to pick up unsuspected adverse reactions in drugs that are very powerful and totally new. This does not concern only the oral contraceptives.

Well, as I told you, this was a hardworking committee, and the Commissioners of the Food and Drug Administration that we worked under were hard driving. Our next assigned task was to write a report on the intrauterine devices.

Do you have that available to your committee?

Senator NELSON. Yes.

Dr. HELLMAN. This again had a deadline. We, I think, did a good job. It pointed out the two very serious difficulties with the intrauterine devices: One, that the devices cause an increase in inflammation of the pelvic organs in about 3.5 percent of the patients in whom they were inserted. This inflammation decreased in the second year of use, but it still is an adverse effect.

Senator NELSON. Did you say 3.5 percent?

Dr. HELLMAN. 3.5 percent.

Second, there were some deaths associated with the intrauterine devices that, up until the time our committee worked on it, had passed unnoticed.

Now, again, we are dealing with a very poor data base and we have to make some assumptions. We wrote to every obstetrician and gynecologist in the United States and asked them about the serious adverse reactions with the intrauterine devices, especially deaths. They were very cooperative and we got something like an 85- or 90-percent reply to our letters. Very few of them refused to give us total informa-

tion and 10 deaths with the intrauterine devices were reported, we thought, to perforation of the uterus at the time of insertion of the device, peritonitis, and intestinal obstruction.

Senator NELSON. May I interrupt a moment?

Dr. HELLMAN. Yes, sir.

Senator NELSON. Then death was not caused by the use of the intrauterine device, but by improper insertion by the physician?

Dr. HELLMAN. Well, I would not use the word "improper," Senator, because any obstetrician and gynecologist who puts something in the uterus realizes that the danger of penetration is quite real. This happens to all of us.

Senator NELSON. Just so the record is clear, it was not caused by the presence of the intrauterine device?

Dr. HELLMAN. That is correct, yes, sir.

In order to make an estimate of the frequency or prevalence or incidence of death, we had to estimate how many intrauterine devices were used in the United States. At that time the most sophisticated estimate we could come up with was about a million were in place in the United States.

We said, "Well, we have 10 deaths reported, let's say we made a 50-percent error and there were probably 20." So we came up with two deaths per 100,000 or 20 per million.

It is interesting, that although the Food and Drug Administration does have authority over devices as well as drugs procedures equivalent to those for drug approval do not exist for the approval and surveillance of devices. Therefore, direct action for the implementation of the recommendations in this report by the FDA was less feasible. Nevertheless, we made two specific recommendations.

One was that packaging of the intrauterine devices be improved. The way they were packaged before was that the device was separate and the inserter was separate and then they had to be sterilized and then the device placed in the inserter. All of this gave a chance for contamination. We recommended that packaging be sterile and that the device be in the inserter so there was little chance for contamination. I am very pleased to say that this recommendation was followed by a great many of the manufacturers.

The second recommendation we made is that the closed devices—a closed device is a ring that is hollow, and it collapses if you put it in the uterus and then it expands—be eliminated. It was these closed devices that caused the majority of the deaths, because when they perforated the uterus, they produced a hole through which a loop of bowel entered and then the bowel became obstructed. The closed devices are no longer used in this country.

Senator NELSON. There is continuing research. Has that been improved since your last report?

Dr. HELLMAN. There is a good deal of research on whether you can get a better intrauterine device, one that will not be extruded spontaneously and still do the job. There are almost as many devices as there are investigators, and I would have to answer you in candor, Senator, that I do not think there is much improvement in these devices at this time.

The third report of the Committee, which was issued, again against a deadline, the deadline being August 1969, I think is a scholarly re-

port. It reflects the increase in information. We had a good many consultants, and we had the benefit of some experimental work that was done by the Committee itself, namely, the Sartwell Report on Thromboembolism.

It differed from the previous report on pills in several respects that I will take up in just a minute. I would like to say at this point that it seems to me that the Food and Drug Administration and the Committee have been more than diligent in an effort to keep abreast of the information available to them. I can find really no fault with this organization. My resignation as Chairman of the Advisory Committee took place in December and was based entirely on my own preference. I told Dr. Ley at the time that I thought it was time for some fresh blood in the Committee, that I had given and said about all I could say in any report, and I hoped he would agree with me and accept my resignation. He did, with reluctance. Actually, it happens that with my new job as Deputy Assistant Secretary, I could not be Chairman of that Committee anymore anyway.

Now, I think also that one can say the same thing for the Committee on Safety of Drugs in Great Britain. They have been hardworking, they have endeavored to keep the public and the press and the scientific community informed.

I think that these three documents, Senator Nelson—and I am not alone in this opinion—constitute the best single body of knowledge on modern contraception that is available today. The distribution of these documents throughout the world, bespeaks this matter.

Now, let us get down to the second report.

Our Committee worked by dividing into task forces. The assignments of the various task forces were discussed at a preliminary meeting. Then the Chairman assigned the various members to the task force. They were allowed to meet at any intervals that the chairmen of the task forces wanted to. The resources of the Food and Drug Administration were available to them, as well as the resources of the pharmaceutical industry. I would like to emphasize here that the industry has always been cooperative with this Committee in any day they could.

When a task force had a rough draft of its report, and this was often very rough, there was a meeting of the Committee and the rough draft was read to the members of the Committee. Suggestions for change were made. When the final drafts or what they thought were the final drafts were ready, there was another meeting of the Committee. The final drafts were read in detail, the data presented, and corrections made by the Committee and approval or disapproval of the report made.

You will notice in the first report that the Committee on Carcinogenesis has two reports. This has often been interpreted as meaning there was a minority and a majority report. I do not like minority reports. I do not think they mean very much. It was not a minority report. There was a real divergence of opinion, and it seemed to the Committee, and they voted so, that both reports should be published. And I think it was very salutary that they were.

Then, after the task forces were in, the Chairman had the task of trying to summarize what was said. This fell to me and it fell three times in succession, during my vacation. I had a little difficulty with my wife on this problem. Nevertheless, when the Chairman submitted

his report, he did so by taking excerpts from each of the task force reports, by talking to the Chairman of the task force during the writing, by mailing a rough copy of his draft to each member of the Committee, then by having a final meeting of the Committee to discuss the summary. They corrected the Chairman's summary as their own were corrected and the final draft was approved by a vote of the Committee as the report of the whole.

Following that, these drafts were meticulously edited and every reference in the second report on oral contraceutives was checked by me personally or my own staff in New York.

Now, there are significant differences between the second report on the oral contraceptives and the first report. The first and most outstanding is that the information about thromboembolic disease was available so that the Committee would say without equivocation——

Senator NELSON. May I interrupt? What was the date of the first report?

Dr. HELLMAN. The date of the first report was August 1, 1966.

Senator NELSON. And the second one?

Dr. HELLMAN. The second one was August 1, 1969. The Committee can say without equivocation that there is a relation between the oral contraceptives and thromboembolic disease. This relation had been established by three studies in Great Britain, first by the general practitioners study, second by a retrospective study conducted by Dr. Doll and Vessey, and third by a study of deaths in Great Britain due to thromboembolism. It was reinforced by the Sartwell study, which was conducted by Dr. Sartwell, who is a member of our committee and who is professor of epidemiology at the School of Public Health at Johns Hopkins.

It is interesting, I think, that without any communication between us and the British group, the design of the two retrospective studies was exactly the same. In essence, what we both did—both groups did—was to select patients of childbearing age, between the ages of 15 and 44, who were in hospitals for thromboembolic disease that was idiopathic. By idiopathic, we meant strictly defined thromboembolic disease without any known cause—such as an operation, an accident, obesity, pregnancy, and so forth. These patients were matched with controls. Our matching was a little bit different, but the controls were selected roughly within the same age group, married women, the same race and the same number of children. In the United States, we endeavored to get the same economic classification; namely, were they ward patients in hospitals or were they paying patients?

These four reports together enabled an estimation of the risk of death; namely, about 3 per 100,000 users. They also estimated the risk of hospitalization, of getting thromboembolic disease. The British reports said 1 in 2,000. They said excess risk, and by that we mean risk over normally occurring disease. They estimated the excess risk between 7 and 9 times. Our estimation of the excess risk of thromboembolic disease was about 4½ times. There is no significant difference between these estimates. They may sound a little different, but they are in the same ball park. It is quite possible that thromboembolic disease itself not related to oral contraceptives has a different incidence in different countries. For instance as far as we can tell, it is extremely rare in tropical countries, almost unheard of in India. So these differences are minor and need not concern us.

Mr. GORDON. Dr. Hellman, is it reasonable to assume that they are different in two countries like Great Britain and the United States, similarly situated as far as climate?

Dr. HELLMAN. Mr. Gordon, I think it is reasonable. There is a funny thing that has happened with thromboembolic disease that none of us understands. In about 1960, the incidence in Great Britain and the United States began to rise. It began to rise in both males and females. This is apparent in our own vital statistics reporting and that in Great Britain. This is idiopathic thromboembolic disease, no known cause. We have no explanation for this whatsoever except if I had to make a guess, I would say perhaps people do not walk so much as they used to and maybe the automobile is responsible.

Mr. GORDON. In both countries, though?

Dr. HELLMAN. In both countries. Now, the difference in the rise is not the same in both countries. I think any time you have different populations, you can expect a different incidence. I would not put too much emphasis on this point.

At the time that the British data were first available I happened to be in Great Britain and had the data firsthand. They were very cooperative with us. The Food and Drug Administration called a meeting of our committee and a meeting with representatives of the pharmaceutical industry. We placed this information before them and changed the labeling of the oral contraceptives, in spite of the fact that our own study was not available. In the labeling, we indicated what the British results were. We said at the time that we could not, in honesty, translate the British results to the United States.

Senator NELSON. When you say "labeling," you are referring to the package insert?

Dr. HELLMAN. Package insert. I guess "labeling" is a little slang for this, but that is what is used.

When we get to the other areas that the Committee considered, they considered utilization and efficacy, again we had a little better information than we had before. We had made some estimates of utilization, how many people were using the oral contraceptives, in the first report, and we made some projections for the future.

However, we found that we had underestimated the use. We had estimated in 1966 that by the year 1969 there would be about 6 million women using the oral contraceptives in the United States. Our figure in the second report is 8.5 million.

This piece of data is not quite as solid as I would like to have it be, because we have no way of really finding out how many people use what in the United States. So what we did was to take the sales and distribution figures from the pharmaceutical houses and by a formula that they use, and that I think is acceptable, get some idea of the usage. That is how this 8.5 million figure is arrived at. I do not think it is far wrong; but I wish it were a little better. The world usage figures again have the same limitations, but somewhere between 10 and 12 million women outside the United States use these compounds.

Senator NELSON. 10 or 12 million in addition to——

Dr. HELLMAN. About 18 million people in the world probably use these compounds now. Most of them, as you might imagine, are in the developed countries. The problem in the undeveloped countries with the oral contraceptives, as far as I personally know it, and I know

India and Nepal and Iran personally from having been there for AID, is a difficult one. As you know, these countries have governmental family planning programs. They are thoroughly familiar not only with these reports, but also with what has appeared in the news media. And as a result, they are reluctant to use for a national program, products for which we have emphasized certain hazards. Now, I can understand the politics back of this, but I also think from the world situation as far as population goes, this hesitancy may have regrettable effects.

When I was first in India 2 years ago, there were 500 million people. When I was in India last year, there were 534 million people. I think India will have a billion people by the time we turn the century.

Now, one of the things that the Committee went into for all contraceptives is what is called the continuation rate. That is, if you start a person on a contraceptive, how long does she continue to use that contraceptive? This is very important.

We have these data for the intrauterine devices because the Population Council instituted a cooperative research program for the intrauterine devices at the same time that the devices were introduced. This was a very well thought out investigative program conducted by Dr. Christopher Tietze, who is a genius at such studies, so we know the continuation rate for the IUD. We know that about 80 percent, perhaps a little less, continue to use the intrauterine devices after the first year, and it drops approximately 10 percent per year thereafter. The continuation rate of the oral contraceptives is not anywhere near as well known, and our estimates again by Dr. Tietze, are that about three-quarters of the women who start on oral contraceptives continue to use them after the first year; about 60 percent after the second year, and it is down probably well below 50 percent at the end of the third or fourth year.

Senator NELSON. Fifty percent?

Dr. HELLMAN. Fifty percent. So that the continuation rates of the oral contraceptives are not quite as good as the continuation rates of the intrauterine devices.

Mr. GORDON. Doctor, Dr. Hugh Davis, who testified before our committee last week, stated that a Chicago study of this by Dr. Frank found that 40 percent of those patients started on oral contraceptives had abandoned them after 2 months, and at the Maryland Planned Parenthood Clinic, half of the patients abandoned them in less than 1 year's time.

Are you acquainted with those figures?

Dr. HELLMAN. I am acquainted with those figures. That is one of the troubles in this field, Mr. Gordon. You can get all kinds of information, and to put it together and get a general picture, is difficult.

What I said to you is that our data are the best that Christopher Tietze could put together.

In my own experience in our family planning clinic at the State University, which I said to you was a very large one, has been divergent from some of the reports that we quote. The reason that you get differences is this: In the first place, it depends on the population. If you have a highly motivated population, you can get good continuance. If you have a nonmotivated population, you get poor.

The second difference is you must, to continue contraception in any group of people, have available medical services to which the people

can come at a moment's notice. In other words, if you are running a clinic, you have to have some way for the person who has difficulty to talk to either a doctor or a nurse or somebody. If you do not have this, the continuation rate is very poor.

Let me give you an example. It is an exaggerated example but I think it is a good one.

We visited a small village in India where they were using oral contraceptives. I suppose this village had 250 women in it. They had 25 women on the oral contraceptives and everybody was happy. But they did not have a doctor there on a full-time basis or a nurse. One of the women, the wife of the leader of the village, had an episode of diarrhea, nausea, and vomiting. These are common in India. But she was on the oral contraceptives and she told all her friends, and in the second day we had 12 dropouts, and in the third day nobody was taking the oral contraceptives. So this is the kind of thing that you get if you do not have medical care readily available.

Mr. GORDON. Dr. Hellman, when you talk about use effectiveness, you do consider the dropout rate?

Dr. HELLMAN. Yes. This is a difficult question, Mr. Gordon, for the nonprofessional to understand. We have two kinds of effectiveness that we talk about.

Mr. GORDON. I am talking about use effectiveness, not theoretical effectiveness.

Dr. HELLMAN. Has this all been explained to this committee?

Mr. GORDON. Yes.

Dr. HELLMAN. Then we will not go into it. Use effectiveness takes into account the dropout rate.

Mr. GORDON. Then would you consider, with the dropout rate in the figure, that the use effectiveness of the IUD is higher than that of the oral contraceptives?

Dr. HELLMAN. I cannot do that mathematics that quickly, I am sorry. I just cannot answer that question.

Mr. GORDON. Can you supply that for the record?

Dr. HELLMAN. Yes, I will if you would like.

(The information follows:)

2D REPORT ON THE ORAL CONTRACEPTIVES ADVISORY COMMITTEE ON OBSTETRICS AND GYNECOLOGY—FOOD AND DRUG ADMINISTRATION, AUG. 1, 1969

PREGNANCY RATES PER 100 WOMEN PER YEAR

	Method [1] failures	All [2] pregnancies
Oral contraceptives:		
Combined regimen	0.1	0.7
Sequential regimen	.5	1.4
Intrauterine devices:		
Large Lippes Loop	[3] 1.9	2.7
Saf-T-Coil	[3] 1.9	2.8
Condom or diaphragm	2.6	
U.S. clinics:		
Diaphragm used with spermicidal jelly or cream		17.9
Vaginal foam		28.3
Vaginal jelly or cream alone		36.8

[1] Sometimes referred to as "theoretical effectiveness;" it is nearer to being the "theoretical ineffectiveness."
[2] Sometimes referred to as "use effectiveness;" it is nearer to being the "use ineffectiveness."
[3] Pregnancies with IUD in situ. All rates for IUD's and traditional methods are for the 1st year of use.

Note: The "use effectiveness" of the combined regimen of the oral contraceptives is about 4 times that of the IUD; and the "use effectiveness" of the sequential regimen of the oral contraceptives is about twice that of the IUD.

Dr. HELLMAN. Actually, there is no standard, Mr. Gordon, about how you count the dropouts. This has been one of the difficulties in getting comparable data. The best method now available is to use the life table method, which takes into account the months of use by the dropout and so on. When we get away from these two bits of information, the effectiveness and use, then we get much less precise data. We have two major fields that we have to consider; namely, carcinogenesis and the metabolic effects. And I do not believe, sir, that I want to cover in great detail for you anything more than I have covered in my summary, because I think Dr. Hertz covered carcinogenesis, and you have an eminent scientist here, Professor Wynn from England, who is going to cover some of the metabolic effects, and also Dr. Goldzieher who will testify before you today, and some others, I believe, have testified in the past.

Now, not reading from the record but just talking to you about carcinogenesis, we were up against a formidable problem. In the first place, we have had estrogen available to the medical profession since 1930, naturally occurring estrogen to be used to treat people. Almost since its inception, it became apparent that if you gave this compound in sufficient doses to experimental animals—laboratory animals, and five species were tested, as Dr. Hertz told you—you could produce carcinoma, cancers. The argument used by people who used estrogen—and I am not talking about estrogen for contraception; it was used for a lot of other things, used particularly to treat post-menapausal women. The argument used by doctors was that they had treated a great number of women, that they had not noticed any increase in cancer of the uterus or cancer of the breast, and that it would be unfortunate, indeed, if laboratory experiments were transposed directly to man. I think a biologist such as Dr. Hertz finds great difficulty in accepting this argument. And I must admit, myself, I have some unease about it, because it seems to me that biological systems must work according to the same general rules, and that whereas you may have species differences, resistance differences to certain diseases, and there are species differences in the resistance to cancer induced by estrogen, that in general, the same rules ought to apply. All of us who are responsible obstetricians and gynecologists who give estrogen to women, whether we give it for contraception or other reasons, always do so with the thought in the back of our mind that these are powerful drugs and that they may have an adverse effect, and we continue to keep these women under surveillance if we perform our task properly.

As Dr. Hertz indicated to you, there are some paradoxical reactions of cancer in human beings to estrogen and we cannot explain these. For instance, the removal of ovaries in women with cancer of the breast if they are premenopausal cures or delays metastases in between 30 and 50 percent. On the other hand, if they are after the menopause you can get amelioration of metastases by giving estrogen. I do not believe we have any explanation of that.

Mr. DUFFY. Doctor, could I ask you to comment for a moment on some of Dr. Kistner's comments about cancer?

It appeared to me—as a matter of fact, I might quote from the record, which is not an exact quote but just my remembrance, that Dr. Kistner said that he could not prove that Dr. Hertz was right, that

he could not prove that he was right, and neither one could prove that the other was wrong. It seemed to me at that point that we had a sort of medical standoff. Very responsible opinions differ with one auother, and the issue sort of was left with the question that we needed to test a good bit more before anybody could really address the question with a positive answer.

Dr. HELLMAN. I think in the first place, these two men are both eminent people. They both spoke the truth. They look at it from a different viewpoint. Dr. Hertz is in essence a biologist who looks at fundamental mechanisms. He is a laboratory man. Dr. Kistner is a clinician, and clinicians look at these problems a little differently.

Actually, what they were talking about was a tumor that probably does not really come into very serious consideration with the oral contraceptives, namely cancer of the lining of the uterus. It is possible that the administration, periodic administration of steroids might alleviate this tumor.

I think you are right when you say there is a difference of opinion and it has to be resolved by some very carefully worked out long-term research.

Now, we have another problem besides the animal problem.

Senator NELSON. Doctor, a few moments ago you pointed out that estrogens have been used for the treatment of disease since the thirties.

Dr. HELLMAN. Yes.

Senator NELSON. Are estrogens for the treatment of disease used in the same quantities as for contraceptive purposes and over the same long, sustained period of time?

Dr. HELLMAN. Menopause is the one area where there is a lot of treatment with estrogen, and it is usually treated with naturally occurring compounds and not synthetic compounds. The comparable dosage, and this is very difficult, is probably somewhat less in most cases. The length of time of treatment, however, is pretty long, because it can go from the age of 45 to 70. The data that we have available, and the committee may not have seen this, and I will submit it for the record, goes back to 1958, and this is taken up until 1966. I suppose we have 1967 data available. It records the deaths from cancer of the breast, cancer of the neck of the womb, the cervix, and cancer of the body of the womb in the United States. I will pass this up if you wish it.

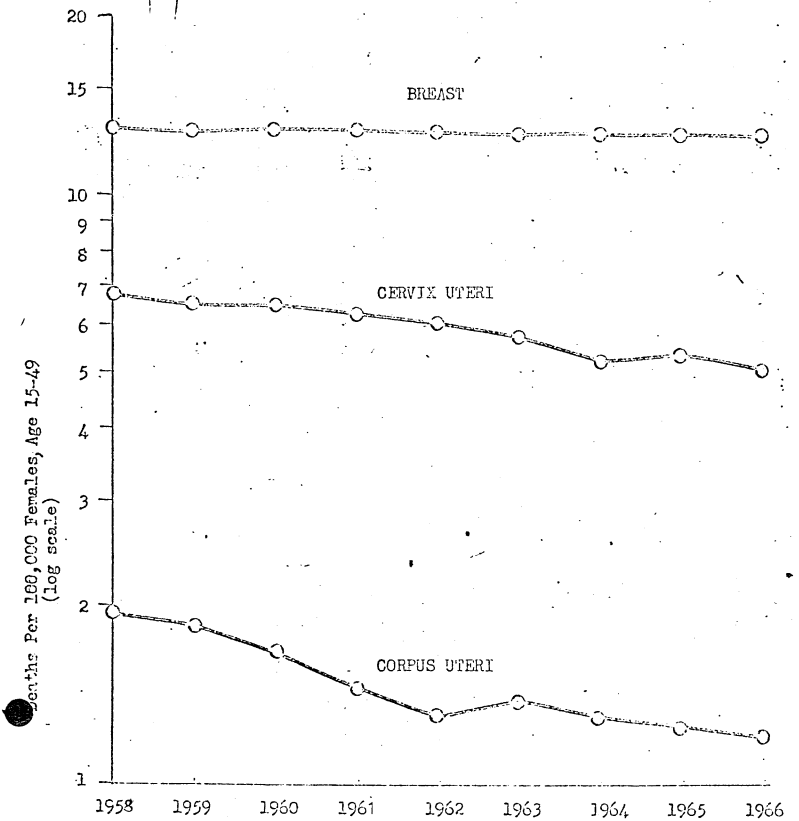
Senator NELSON. It will be printed in the record.

(The document referred to follows:)

FIGURE 3

MORTALITY FROM CANCER OF THE BREAST, CERVIX AND CORPUS UTERI

United States Females, age 15-49, 1958-1966



Dr. HELLMAN. What it shows is that there has been no change in cancer of the breast, in decrease of deaths from cancer of the neck of the uterus. Now, I do not think that these data reflect the oral contraceptives. And this brings us to the next serious problem.

Mr. GORDON. Dr. Hellman, you stated on page 17—you are not reading?

Dr. HELLMAN. I am not reading; no, sir.

Mr. GORDON. You stated, "* * * the problem of the possible carcinogenic effect of the oral contraceptives on the breast is worrisome and unresolved."

I gather you are sort of uneasy about the situation. You used the word "uneasy" before.

Dr. HELLMAN. I think that that is a good word. I will stick with it.

Mr. GORDON. So much so that you stated on August 1, 1967, you said that, "If I were a young lady these days and had any fear of cancer, I would probably use an intrauterine device." That is your statement right here.

Dr. HELLMAN. That reminds me of a statement my wife once made, that Dr. Hellman talks a lot and I cannot keep track of everything he says.

That was an interview, as I remember it, and the question posed to me was if you had a patient who came in to you and was very much afraid of cancer, would you prescribe the oral contraceptives? Under those circumstances, with this information, I would not prescribe the oral contraceptives. I think you have to treat a patient and her emotional standpoint. If the contraceptive she uses is going to scare her, I do not think that is the way a physician ought to treat a patient.

Mr. DUFFY. Doctor, in other words, it is your testimony regarding this point that this quote is taken somewhat out of context?

Dr. HELLMAN. I beg your pardon?

Mr. DUFFY. I asked is it your testimony in answer to Mr. Gordon that this quote of yours is taken somewhat out of context.

Dr. HELLMAN. Well, it is a true quote. I remember saying it, but, yes, it is a little out of context. I would say the same thing today if the same question were asked.

I was coming to Mr. Gordon's point, because this brings up the next issue. As I said to you, these data in this graph do not reflect the use of the oral contraceptives in the United States. The reason that they do not reflect it is that when you give a known carcinogen—take X-ray, aniline dyes, Pyribenzamine, a number of things that are known to cause cancer to human beings—with any biological system, you have a delay between the initiation of therapy and the onset of the cancer. In humans, it is estimated that the mean delay would be about 10 years from the introduction of a carcinogen.

Now, we have not used the oral contraceptives in any great degree for 10 years. Furthermore, you would have a delay between the onset of the disease, if you give a carcinogen, and the death. And death might be delayed again from anywhere from 2 to 5 years depending on the type of therapy the patient got. So if you add all these things together, it is unlikely that the vital statistics of the United States will reflect any change, if there is one, from the oral contraceptives until the mid-1970's or so. These are very encouraging bits of information, but they do not bear on the subject.

Now, I think that we have some reports. Dr. Hertz covered with you the study, from the Sloan-Kettering Institute, on the cervical changes due to oral contraceptives. He probably covered with you the difficulties of that study and the criticisms leveled at it.

I think the Committee, in analyzing the situation, came to this conclusion, and I will read here, because I do want to be accurate about this point—"lacking conclusive information about the applicability of animal data to women and valid direct observations on human beings, the potential carcinogenicity of the oral contraceptives can neither be affirmed nor excluded at this time. Suspicion, however, continues and has been enhanced by recent cytologic studies of the cervix. It is therefore necessary that a major effort be expended to solve this problem. In the meantime, clinical surveillance of all women taking oral contraceptives must be vigorously continued."

That latter appears in the labeling and in the letters that have gone out, and in most of the medical literature.

Senator NELSON. Do you have any guess, statistics, or figures of your own that will indicate what percentage of the women who are using the pill have a regular physical examination?

Dr. HELLMAN. No; I do not have very good data for you. I can tell you this—I have some data. I can tell you this, that in the contraceptive clinics of New York City, my own in particular, which I said deals with economically deprived individuals, the periodic examination is meticulously carried out. Now, we do move some patients. They move, they do not come in, but we try to get them by telephone calls and so forth.

In Maryland, Dr. Davens, who is acting commissioner of health, assures me that the—and I choose Maryland because it is one of the best organized States for treatment of clinic patients with family planning—assures me that the follow-up is good.

Now, I knew you were going to ask this question, so I initiated a small research effort of my own. I am sure you will realize that it is not very meaningful, but I have a farm up in Maryland, in rural country, and the local pharmacist is a friend of mine. I asked him about 3 or 4 weeks ago whether he would ask the patients who came in with prescriptions for oral contraceptives whether they had been warned of the dangers and whether they had periodic examinations. These are all general practitioners. There are no specialists in this area.

This is a difficult question for a pharmacist to ask, because if the doctor finds out he is asking the question, he will call him up and say, "What business is it of yours?" He felt he could not ask them about the periodic examination, because the patient would have said immediately, "Should my doctor be doing that?" But he did ask them about warning. We got 10 patients and all but two of them had had a thorough discussion with the doctor about the potential hazards.

Now, this is a small sample in a tiny town in Maryland. I do not know whether it means anything or not, but investigation of this kind can be done, I think, and ought to be done.

Senator NELSON. I have been told by two pharmacists that they did not have any statistics on the frequency, but that frequently or regularly they will see a prescription—they did not give me any percentage—which simply is to be filled upon request.

So the users carrying the prescription can get it filled on request. Now, they still may be getting the examination, I do not know, but this might raise a question as to whether they were.

Dr. HELLMAN. It can raise a question. I cannot speak for the medical practice in the United States, but I think all of us know that there are areas where it is excellent and there are areas where some change would be good.

I think one thing comes clear in these data that does not have anything to do with oral contraceptives. This is the decrease in deaths from cancer of the uterus in the United States since 1958.

Now, the disease has not changed. This can only mean that the cancer smear programs which are being carried out vigorously and the information being conveyed to all women, regardless of whether they are on the contraceptives or not, that they should have these examinations has been effective.

I know in my own practice, and it is tiny, but if I did not make periodic appointments with patients, they would call my secretary and want to know what is the matter. I am sure this happens very, very frequently.

Now, I think it is wrong to take the time for me to talk about the metabolic effects of these pills when we have some experts here who are going to testify on this very point. I will say this, that the committee, the task force under Dr. Corfman reviewed about 3,700 references to write the review that they wrote of the metabolic effects here. It is quite apparent, and I think somewhat unexpected to those of us who have lived through the development of the steroid hormones right from the beginning, that the hormones had such a widespread metabolic effect on the body.

Now, Dr. Wynn will talk to you, I believe, chiefly about the two that we know most about, namely, the effect on the use of sugar by the body and the effect on body fats. There are some others that we know a good deal about.

Again, the committee is faced with some biological data, meaning that certain things have been changed in the human body when you take oral contraceptives. These things also change for other reasons.

One of the things they change from is pregnancy. The carbohydrate metabolism is changed in pregnancy, the fat metabolism is changed in pregnancy, the levels of circulating fats go up.

What we do not have is the answer to the question, do these changes signify any health hazard to the individual? The committee has always been forthright in its statements and when it did not know, it said it did not know—said, "We do not know. We have to keep this matter under investigation."

I think it is heartening that the number of investigations into the metabolic effects of the steroids has multiplied tremendously. It has not only multiplied among the private sector and the scientists and doctors, but the drug houses themselves are carrying on a tremendous amount of research in this very area.

Senator DOLE. Dr. Hellman, when did you first prescribe the pill?

Dr. HELLMAN. Probably right after it was first introduced.

Senator DOLE. I just wonder how many patients you see now or how many you have seen personally who are "on the pill."

Dr. HELLMAN. Yes, sir.

Senator DOLE. How widespread has your own experience been?

Dr. HELLMAN. It is fairly widespread, sir, because we have a very large clinic. Although I do not see all these patients personally, I see the data. As I said to you, there are 4,000 new patients a year come into this clinic for family planning. The figures are as follows—and I got them last week for you:

Of the patients in this group, 55 percent have intrauterine devices; 40 percent are on oral contraceptives; and 5 percent are on traditional methods of contraception, mostly the diaphragm.

Senator NELSON. How do you account for that statistic when I understood you to say earlier that there were perhaps a million people on the IUD nationally and 8.5 on the pill? If it is 8.5 to 1, why, in your clinic, is it 55 percent IUD and 40 percent on the pill?

Dr. HELLMAN. I have a man in my department who has developed an intrauterine device who works in this clinic. I think this is the answer.

Senator NELSON. I am sure you are not saying he prescribes it because he has it.

Dr. HELLMAN. Well, I think seriously, he believes that this is a very good device and a very effective one.

Senator DOLE. You have had a chance, then, many opportunities to personally observe or study the side effects, whether it is diabetes or thromboembolism or cancer. What have been the side effects, in your personal experience, as far as your own patients are concerned?

Dr. HELLMAN. My private patients have had no serious adverse effects from the pill. They come off the pill because of a host of minor reactions. The most prevalent one is weight gain. The modern American girl just does not want to gain 5 or 10 pounds if she can help it.

Other reasons are breakthrough bleeding, headaches, and a general complaint that these pills "made me feel pregnant all the time and I do not want to feel that way."

Some of them have come off the pill because of what they have read in the press or what their husbands have read in the press. Each time that one of our reports came out or the newspapers begin to print information, we always get a significant withdrawal of patients from the oral contraceptives. Whether they come back or not, I do not know.

There are interesting data in this regard: I have been bombarded by obstetricians and gynecologists around the United States since your committee has been meeting because they are being bombarded by their patients and they want to know whether there is anything different coming up.

I checked in our clinic last Monday or Tuesday, and asked whether we have had any withdrawal of patients from the oral contraceptives in the clinic. Strangely enough, we have had none. Now, I have no explanation for this except that we are treating patients from the ghetto and they think of us as the "establishment" and they do not believe what we say.

Senator DOLE. In this group, I think you mentioned 55 percent used IUD's, 40 percent the pill.

Dr. HELLMAN. Yes.

Senator DOLE. How do you personally compare the side effects of the IUD versus the pill? You mentioned that the IUD has some side effects earlier.

Dr. HELLMAN. Yes.

Senator DOLE. There has been, of course, great use of IUD's in India and Pakistan. I have been there and seen some of the clinics in areas where they are trying to promote the use, without much success, frankly. Is it any less safe with the pill than it is with IUD as far as certain side effects or risks are concerned?

Dr. HELLMAN. If you will let me, I want to close with the discussion of safety. But I will say this, that if you just number the complaints that you get—not talking about the serious problems, but the complaints the patients give you—you get about as many with the IUD as you do with the pill. And with both methods of contraception, you have to do what I emphasized before. If you are going to treat a population, you have to have available to them constant medical information. You have to have somebody they can talk to; otherwise the thing will happen that happened in India. They had a good start on an IUD program and it just went right down. They do not have the personnel, the manpower, or the organization to carry out these things.

Senator DOLE. Let me have just one further point here. I read what you indicated with reference to discussing side effects with the doctor and the information needed. It has also been suggested that perhaps there should be some written information available to the user. How are we going to do this in a way that can be understood and still be brief enough to attract the attention of the user and be really of any benefit at all?

Dr. HELLMAN. Well, there are pamphlets that are put out by the drug houses that supposedly give patients information in language that they can understand.

Now, I would like to have delayed any discussion about these until Dr. Edwards testifies because he has gone over them much more carefully than I. There is a question of how much FDA can regulate what is put in these pamphlets. But if you would, I would like to have you ask Dr. Edwards that question, and not me.

Mr. Gordon asked me whether I would discuss the conclusions of the report with regard to safety, and I shall now do this as the closing business.

In the first report, in the chairman's summary—it is not labeled "chairman's summary" in that report, but it is the chairman's summary—we had to make some statement about safety. This was at the request of the Commissioner, and as you know, he is charged with both the efficacy and safety of drugs. It is quite apparent, if you read the report, even the first report, that the committee recognized certain very serious problems with oral contraceptives. They, however, were unwilling, and rightly, I believe, to say these things ought to come off the market. And they were faced with the dilemma, you have to make the statement.

Now, the statement we made in the first report said that these compounds are not unsafe for human consumption, which may not be the exact words, but that is what was said. That is a cute statement, more than a good statement, because we use the double negative to imply doubt. I never was very happy with that statement. I think it is kind of like the Delphic Oracle. You ask him what did you say, we did not understand it, and it is just about like that.

I always, in discussing that, said what this means is there. Is a yellow light of caution being exhibited by this committee?

Now, in discussing the chairman's report, the second report, with the committee, I said to them that a more forthright statement has to be made. We cannot just hide behind rhetoric. We are going to have to say something. And we had options. "These are not safe," and then the Commissioner might have to take them off the market if he believed us. We can say "these are safe," and our scientific data did not really permit that kind of statement.

I took it upon myself to look into, as I am sure you have, the Kefauver-Harris amendments that regulate the actions of the Food and Drug Administration at the present time. As I indicated here, although those amendments are specific when they talk about food additives and were made much more specific by the Delaney amendment, which talks to this point. When they talk about safety of drugs, they face the same kind of dilemma that the committee faced.

They say safety pertains to the health of human beings.

Now, the Congress, the 88th Congress, was perplexed about this point and they called the Commissioner to a hearing to testify. What the Commissioner pointed out was very obvious, that any drug, no matter whether it is sold over the counter or whether it is sold by a prescription, if it is effective, it is going to have adverse reactions, and no drug can be absolutely safe.

And I give you but one example of a very pervasive drug sold over the counter, aspirin. We had in the United States in 1967 approximately 200 deaths from aspirin.

So that you keep coming up against this problem. The Commissioner said in his testimony that the safety of a drug cannot be weighed on any yes-no, black-white answer, but must be weighed according to the ratio between benefits and risk.

I therefore wrote the sentence that has caused you and Mr. Gordon and other people some difficulty. I take full responsibility for writing the sentence, "Safe within the intent of the legislation." But I did have consultation in writing that sentence. I did not just dream it up sitting up in Maryland. It was read to the committee and discussed. They approved it but they said, you must clear this statement with two people. It must be cleared by the Commissioner of the Food and Drug Administration, and it must be cleared with legal counsel of the Food and Drug Administration.

Mr. Goodrich and I went over the statement and he said that it was OK, and obviously I discussed it with the Commissioner.

I do not know anything other that I could have said about the oral contraceptives. I think it implied, that there are problems with these drugs. And if you read this report, you cannot escape the fact that there are problems. I think, though, that you have to look at benefits.

Now, benefits are of two kinds when you are discussing a drug. There are benefits to the population as a whole. I do not want to go into the population problem, but I will say that the introduction of modern contraceptive methods has made the problem of population control immeasurably easier. With the traditional methods of contraception, it is very difficult, as you must have seen in India, to get any response out of the impoverished people. They have neither the time nor the privacy

nor the motivation to use diaphragms, condoms, or whatever you will.

So much for population, except I think, Senator Nelson, you spoke the other day on pollution. If we do not control population in the United States, whatever other legislation for human welfare we enact will be useless if we have 100 million more people by the turn of the century.

Now, personal benefits. There are a great many women—I cannot make an estimate—but there are a great many women in the United States for whom an additional child to the family would constitute a hazard. Let me give you but one example: A patient I saw about 2 weeks ago who had a pulmonary embolism—she did not die—from the oral contraceptives. Therefore, she could no longer take the oral contraceptive. She is colored; she came from a ghetto area, she had two children. Her husband had a poor job. But she had managed to get a job herself and to go to night school to complete her high school diploma.

When we got through discussing her pulmonary problem and the oral contraceptive, she said to me, "Doctor, what can I use that will be as sure as these contraceptives? Because another child would put me right back down on welfare."

Now, this is an exaggerated example, but I can recount hundreds of these. It seemed to the committee and it seemed to me that the ratio of risk to benefit at the present time was sufficiently high to fit into the intent of the Commissioner's testimony before the hearings of the Congress. That is why I wrote this.

Thank you, sir.

(The complete prepared statement of Dr. Hellman follows:)

TESTIMONY BY LOUIS M. HELLMAN, M.D.*

Mr. Chairman and Members of the Subcommittee: It is a pleasure to appear before your Subcommittee to discuss the oral contraceptives. I am Dr. Louis M. Hellman, Professor and Chairman of the Department of Obstetrics and Gynecology of the State University of New York, Downstate Medical Center; Director of Obstetrics and Gynecology, Kings County Hospital; and Obstetrician Gynecologist in Chief, State University-Kings County Hospital Center. From November 1965 through December 31, 1969, I served as Chairman of the Advisory Committee on Obstetrics and Gynecology of the Food and Drug Administration. At present, I am Deputy Assistant Secretary for Population Affairs, Designate, of the Department of Health, Education, and Welfare.

The Food and Drug Administration's Advisory Committee on Obstetrics and Gynecology was established in November 1965 with the mandate to evaluate the modern methods of contraception with particular emphasis upon the oral contraceptives. The Committee attempted to review the vast scientific literature on the subject, and to arrive at impartial decisions based solely on scientific evidence. Wherever the evidence was definitive the Committee made definite recommendations. Where the evidence was lacking or inconclusive the Committee attempted to deliniate the issues as clearly as possible.

Since its inception the Committee has issued three reports:

FDA Report on the Oral Contraceptives, August 1, 1966
Report on Intrauterine Contraceptive Devices, January 1968
Second Report on the Oral Contraceptives, August 1, 1969

Women in the United States have continued to use oral contraceptives in increasing numbers despite some alarming reports in the national press. Physicians have likewise continued to prescribe these contraceptives despite conflicting scientific publications concerning their deleterious effects. Possibly the women and the physicians do not believe what has been published or more probably, they have decided that the benefit to risk ratio is sufficiently high to merit continued and expanded use.

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This essay seeks to clarify some of the facts and unknowns that mould attitudes toward the hormonal contraceptives at the beginning of their second decade of use. It further seeks to plot a reasonable course for family planners besieged by a welter of conflicting scientific and lay opinion. The information and attitudes expressed here are largely drawn from the Chairman's report in the Second Report of the Advisory Committee on Obstetrics and Gynecology to the Food and Drug Administration on Oral Contraceptives. Opinions expressed are, however, the beliefs of the author and do not represent any official policy of a governmental agency.

By early 1969, 20 preparations of oral contraceptives (combined and sequential) were being distributed in the United States at the rate of approximately 8.5 million cycles per month. This estimate of use for 1969 is twice as high as that listed in the National Fertility Survey of 1965. It is one-third higher than that published in the report of the FDA Advisory Committee on Obstetrics and Gynecology in 1966. The apparent increase in numbers reflects not only an expansion in the population of women aged 15–44, but a wider use among older women and those of limited education. Such a trend could have been forecast from population estimates as well as from the increase in contraceptive services available in the poorer areas of our big cities. Expanding use of the hormonal contraceptives will probably continue when the recently projected governmental programs are initiated.

The use of oral contraceptives has spread in foreign countries as well. Among countries without laws prohibiting the distribution of contraceptives, only Japan and the U.S.S.R. now proscribe distribution or sale of these drugs. The estimate of worldwide distribution of oral contraceptives is now approximately 18.5 million cycles per month. The introduction of these effective contraceptive agents in some developing countries, however, has been slower than many would wish. Many of these countries have governmental population programs. The constituted authorities have hesitated to introduce massive oral contraceptive programs in view of the widely publicized hazards. Governmental caution in this instance is understandable. The failure, however, to evaluate the benefit to risk ratio may have lasting consequences.

The current aggregate pharmacological experience with the oral contraceptives is unique in that a large percentage of healthy young women is using powerful drugs for a purpose other than the control of disease. This fact alone, irrespective of continuing controversy over the risks, would have provoked attention of the world's press. Particularly in the United States and Great Britain, the press has attempted to keep the public informed of each discovery and each reported difficulty. Such reporting is the duty of a free press; it is the quickest way to satisfy the public's right to know.

The task of conveying complicated scientific information to the public is a responsibility requiring well informed and accurate reporting based on a judicious appraisal of data. Neither the public nor the press is well served if the information is exaggerated, mitigated, or suppressed. In the final analysis, both the physician and the layman must evaluate the risks of the hormonal contraceptives in comparison with those of other methods of contraception, or no contraception at all. They can do so wisely only when they have access to all available information accurately and dispassionately presented.

Not only does the press reflect ambivalence in respect to the oral contraceptives but the scientific literature abounds with divergent reports on the possible relation of these drugs to a host of different risks. The vast majority of adverse effects, however, occur naturally albeit at a very low rate in young women. Thus, identification of an etiologic relation, especially with the more serious reactions, has been difficult and slow. The risk of thromboembolic disease presented by the hormonal contraceptives has now been defined in both Great Britain and the United States. Other risks, such as those of hypertension, liver disease, and reduced tolerance to carbohydrates have not been quantitated with the same precision. Some of the risks have been recognized by isolated clinical observations, whereas others have been predicted on the basis of experiments with animals or merely on theoretical grounds.

Controversy has centered about two areas: the scientific data required to establish an etiologic relation, and the balance between acceptable risk and potential benefit. The voluntary submission of reports by individual doctors to scientific journals, to the pharmaceutical industry, or directly to the Food and Drug Administration, is fragmentary at the best. Since the data on incidence of

the natural occurrence of the disorder in question are not available it is impossible to ascertain whether the haphazard voluntary reporting of an adverse reaction in fact represents an increase in the suspected complication. The limits, as well as the value, of the system of voluntary reporting of adverse reactions have been frequently noted. There is no easy escape from this dilemma, although innovative techniques in reporting of the suspected complication, as for example, cancer, might be very helpful.

It is difficult to separate fact from friction at the forefront of scientific discovery. Evaluation in the area of hormonal contraception has proved formidable to the best informed scientists. The epidemiologic problems are unique requiring refinements in technique not yet fully realized. Case reporting, particularly isolated experiences, is inconclusive. Thromboembolic disease is but one example. Eight years were required from the time of the first reported death to establish the relative risk and an etiologic relation to the hormonal contraceptives. Through perusal of a welter of scientific studies of varied value, the physician is expected to evolve a judgement that will be beneficial and informative to his patient. This difficult course could be shortened and made more efficient by periodic well structured, and responsibly led conferences. The Food and Drug Administration has a similar objective in publication of its Committee Reports. In the meantime, the physician has at least acquired awareness that there are problems, some of which may be serious, associated with the oral contraceptives.

If these problems are so difficult of solution, and if some of the adverse reactions are potentially hazardous, why use the oral contraceptive at all? The answer lies in their effectiveness. The theoretical effectiveness of the combined hormonal contraceptives is reflected in a pregnancy rate of approximately 0.1 per 100 women per year. The theoretical effectiveness of the sequential oral contraceptives appears to be somewhat lower, as indicated in a pregnancy rate of 0.5 per 100 women per year. The usually given pregnancy rates reflecting "use-effectiveness" reach 0.7 per 100 women per year for the combined regimen, and 1.4 per 100 women per year for the sequential regimen.

Effectiveness judged by the total number of pregnancies is significantly better with the oral contraceptives, combined or sequential, than with the intrauterine devices, or any of the traditional methods. The pregnancy rates among users of diaphragms with contraceptive paste thus appear to be 10 to 30 times higher than those among users of oral contraceptives. Similarly, those among users of intrauterine devices are 2 to 4 times higher. Knowledge of the relative effectiveness of the different contraceptive methods helps in the task of balancing the risk against the benefit to the individual and to society. As contraceptive practices spread to all segments of our society, it becomes virtually essential that the requisites of safety, effectiveness, inexpensiveness, and lack of association with coitus be satisfied. The economically advantaged and well educated members of society may be willing to accept a method of contraception that does not entirely satisfy all of these attributes, but the less favored members of society cannot realistically be expected to employ a method, the efficacy of which is in doubt, or use of a technique that requires privacy and special preparation.

Another factor helpful in evaluating benefit to risk is the continuation rate of the selected contraceptive practice. The continuation rates of oral contraceptives are higher than those of traditional methods of contraception such as the diaphragm, and lower than those of the intrauterine devices.

Known risks of oral contraceptives have often been compared with those of pregnancy, cigarette smoking, and automobile accidents. Such comparisons are probably irrelevant and contribute little to the evaluation of relative risks. This evaluation must be made from a knowledge of the relative advantages of the oral contraceptives in comparison with other contraceptive methods or no contraception at all.

Minor adverse reactions to the oral contraceptives, such as irregular bleeding, weight gain, headache, chloasma are well known. Their incidence may not be precisely documented, but their etiology is not in doubt because it has been relatively simple to establish a cause and effect relation and to observe a diminution in the symptoms with discontinuance of the drugs. Visual and emotional disturbances are documented with far less precision. Most of these minor reactions, however, are cared for by simple medical advice. Discontinuance of this method of contraception provides in the most part a satisfactory solution. This type of medical decision involves a few patients and does not require a policy decision necessitated by the potentially more serious adverse reactions such as

thromboembolic disease, fundamental metabolic changes, and potential carcinogenesis.

An etiologic relation between oral contraceptives and an increase in thromboembolic disorders has been disclosed by several groups of investigators using retrospective methods of inquiry. In 1967, The Royal College of General Practitioners in Great Britain undertook interviews of young women who were recorded as having had vascular disease. By comparing patients with superficial thrombophlebitis with a suitably matched series of controls, it could be shown that the risk of developing thrombophlebitis was tripled in women who used the oral contraceptives. In another study Vessey and Doll investigated young women admitted to several hospitals in Northwest London with a diagnosis of idiopathic thrombophlebitis. These patients were also matched with suitable controls. A third study involved all the deaths that occurred in England, Wales, and Northern Ireland during 1966 in women of reproductive age and whose death certificates referred to thrombosis or embolism of the pulmonary, cerebral or coronary vessels. In summary, these studies showed that the chance of hospitalization from thromboembolic disease was about one in 2,000 among users of oral contraceptives, as compared to one in 20,000 for nonusers. Similarly, the mortality rate was estimated at 1.5 per 100,000 users age 20 to 34, and 3.9 per 100,000 users age 35 to 44. Since the publication of these results Vessey and Doll have continued their retrospective study to include a larger group of patients matched with controls. The results of this last study confirmed the previous investigations.

In the meantime, Drs. Sartwell, Masi, and colleagues conducted a retropective study of cases of thromboembolism, and an equal number of matched controls in 5 large cities in the United States. The risk of thromboembolism to women using hormonal contraceptives was estimated by indirect methods to be 4.4 times as that of the nonuser. The excess risk did not persist after cessation of use, nor did prolonged continuation of use enhance the risk. No striking differences among contraceptive products were found except for an excess of the use of sequential compounds among the cases, as compared to control. The findings of the American study are in general agreement with those previously reported from Great Britain.

These studies together establish an etiologic relation between thromboembolic disorders and the use of oral contraceptives. Quantitatively they suggest that the mortality from thromboembolic disease attributable to oral contraceptives is about 3 per 100,000 women per year adding slightly less than 3 percent to the total age specific mortality in users of these drugs.

The hormonal contraceptives produce numerous metabolic changes affecting many organs, for example, the liver, the thyroid, and the adrenal. They also affect some of the body's homeostatic mechanisms; they change salt and water metabolism and occasionally induce hypertension. Recently histologic changes in the blood vessels of some women have been described. In many areas where alternation in function or structure has been noted there is very little basic information regarding the metabolism of the oral contraceptives. For example, little is known of the effects of oral contraception on renal function.

Fears that oral contraceptives might limit the growth, if prescribed for young girls, have proved foundless. These fears were based on observations that large doses of estrogen hasten epiphyseal closure. These observations, however, were based on very large doses of estrogen administered prior to the growth spurt, which occurs somewhere between 10 and 12 years in the United States. It is unlikely that oral contraceptives would be used this early.

The labeling of the oral contraceptives includes a warning to use these drugs with caution in very young girls. This warning is based on an uncertainty about the use of anovulants at the onset of reproductive life. Their effect, however, is probably no more permanent than the suppression of ovulation by a pregnancy.

There is no evidence at this time that any of these drug-induced metabolic alterations pose serious hazards to health. The systemic effects of these drugs, however, are so fundamental and widespread, that continued medical surveillance and investigation is required.

Much indirect evidence suggests that the steriod hormones, particularly estrogen, may be carcinogenic in man. These data are derived from experiments on laboratory animals in which estrogen in particular appeared to cause cancer in 5 species. Although all physical and chemical elements that are carcinogenic in man produce malignant tumors in experimental animals also, evidence of the

carcinogenicity of estrogen in other species cannot be transposed directly to man. Suspicion lingers, however, that the results in laboratory animals may be pertinent to man. Many difficulties arise in epidemiological elucidation of this suspected relation. The principal obstacle is the long latent period between the administration of the known carcinogen and the development of cancer in man. Thus far, no properly devised prospective or retrospective studies provide an adequate solution to this problem.

There are 3 target areas, the cervix, endometrium and breast, that might potentially be affected by the oral contraceptives. It has been known that estrogen produces epithelial changes in the human cervix. The prognosis of these changes is obscure and their etiologic relation to carcinoma is unknown. A recently published study of women attending Planned Parenthood Clinics in New York City has revealed a higher prevalence of cervical epithelial abnormalities that the investigators called carinoma in situ among women using oral contraceptives than in those using the diaphragm. Neither the authors nor the Advisory Committee on Obstetrics and Gynecology of the Food and Drug Administration believes that this study proves or disproves an etiologic relation between the oral contraceptives and these cervical changes.

There is no available data to indicate that the oral contraceptives cause endometrial carcinoma in women.

Although estrogen causes epithelial changes in the human breast, its carcinogenic effect on that organ has never been proved. Even in women with frank mammary carcinoma, estrogen produces variable changes. For example, ovariectomy leads to regression of metastatic breast carcinoma in approximately half of premenopausal women with the disease. It may, however, either cause regression or stimulation of similar tumors in premenopausal women. The reason for this peculiar effect of estrogen on metastatic tumors of the breast is not clear. Furthermore, diagnostic uncertainty surrounds precancerous lesions of the breast; it is not known whether exogenous steroids significantly affect this stage of the disease.

Currently available data on death rates from genital and mammary cancer in women do not clarify the problem of association between steroids and carcinoma. The long latent period of action of known carcinogens (10 years) and the length of time between diagnosis and death eliminate vital statistics as a source of information about this association until the mid-1970's or later.

The massive program of prophylaxis launched against cervical cancer in this country has accomplished a steady decline in deaths from the disease. The common practice of repeating cervical smears, annually or semiannually, in women taking oral contraceptives has contributed to the decline, but it has clouded the question of the effect of oral contraceptives on cervical cancer. There are some who believe that the massive prophylactic program, now common practice in the United States will make exceedingly difficult, if not impossible, an adequate epidemiologic study on the relation of oral contraceptives to cervical cancer. Since there is no method of early detection of mammary carcinoma comparable in efficacy to that of the cervical Papanicolaon smear, the problem of possible carcinogenic effect of the oral contraceptives on breasts is worrisome and unresolved.

Lacking conclusive information about the applicability of existing animal data to women and valid direct observations in human studies, the potential carcinogenicity of the oral contraceptives can neither be affirmed nor excluded at this time. Suspicion, however, continues and has been enhanced by the recent cytologic studies of the cervix. It is, therefore, necessary that a major effort be expended to solve this problem. In the meantime, clinical surveillance of all women taking oral contraceptives must be vigorously continued.

The decisions of the Food and Drug Administration concerning oral hormonal contraceptives are based on efficacy and safety. In the first instance, the issue is clearcut. The second, however, requires a carefully considered approach. Although the Kefauver-Harris Amendments of 1962, under which the Food and Drug Administration derives its current authority, indicate the term "safe" has reference to health of man, nowhere do they define safety. The Commissioner of the Food and Drug Administration pointed out the obvious in 1964 to a Committee on Government Operations of the House of Representatives, namely, that no drug can ever be absolutely safe, therefore, benefit must be weighed against risk in evaluating the safety of the drug.

The risks of the oral contraceptives taken in this light have been under continued surveillance of the Food and Drug Administration. It has periodically reviewed the labeling of these compounds, advocated increasingly strict surveillance by physicians, and recommended the accumulation of additional information about biological actions and clinical effects. As information increases concerning these compounds, both the benefits and the risks appear more precisely defined and quantitated.

Specific risks as well as requisite practices for followup of patients have been detailed in the labeling of all hormonal contraceptives. When the potential hazards and the value of the drugs are balanced, the Food and Drug Administration found that the ratio of benefit to risk was sufficiently high to justify the designation "safe" within the intent of the legislation.

Although this pronouncement by a governmental regulatory agency lends some confidence to the physician and to clinics in their continuing use of the oral contraceptives, it does not relieve them from the responsibility and the decision making inherent in the practice of medicine. As in all other decisions concerning health care, the choice of a contraceptive method rests with the physician and his patient or the clinic policy makers and their patients. It is derived from the knowledge of both physicians and patients and influenced by the complex interreaction between professional and layman. The decision as to which contraceptive to use may be wise or unwise, carefully considered or haphazard, relevant or not, depending on personalities, and on the knowledge possessed by both parties.

As already indicated, there is a vast body of information concerning the oral contraceptives. This information is sometimes divergent and by no means complete. It is, however, far more inclusive and more precise than it was even a few years ago. It does spell out comparative benefits as well as risks where these are known. It enunciates areas of concern and gaps in information. It makes transcendent the need for a high standard of medical practice in the prescription and use of the hormonal contraceptives. An adequate medical history, complete physical examination, including pelvic examination, and Papanicolaou smear, are essential. Annual, or better, semiannual reexaminations with repeated cervical smears are a part of good practice. Open and continuing contact between the giver and the user of contraceptive care are requisite, not only for safety but also for continuation of use. These points are so self-evident, that they seem trite. They are not always observed.

All knowledge and all decision making does not reside with the giver of contraceptive care alone. Increasingly, in all areas of medical care the consumer desires and has the right to information and knowledge about the benefits and risks involved in his treatment. This information is often complex and expressed in terms not always comprehensive to the layman. Especially in the area of the hormonal contraceptives, which are on the forefront of scientific development, knowledge is often incomplete.

Complete disclosure of all available information concerning the benefits and risks of the oral contraceptives would require much more than perusal of the labeling. It would necessitate the years of training and reading that are the hallmark of the professional. This course might be desirable in theory, but it is absurd in practice.

The physician solves this dilemma by conversation in which he attempts to interpret his scientific knowledge in the way that enables his patient to make some sensible choice regarding the preferred method of contraception. The clinic accomplishes the same objective through individual conversations reinforced by group lectures and demonstrations. In the best of situations, the clinic imparts a body of knowledge and fact sufficient for the patient to make an intelligent choice of contraceptive methods.

However, information is given to the user and whatever freedom of choice she may exert, the giver of contraceptive care cannot divest himself of responsibility. No signed release will free him. He can only do his best to impart sufficient information and provide the opportunity to the patient for complete freedom of choice. Meticulous medical care, knowledge and freedom of choice insure neither total satisfaction nor total safety, but they are the best that can be accomplished in an imperfect world.

I thank you for the opportunity to meet with you today. I shall be glad to try to answer any questions which the subcommittee may have.

Senator NELSON. This question of what the word "safe" means in the 1962 act is a difficult one, and I do not know the answer to it. But I

wonder if, in talking about weighing the risks versus the benefits, the word "safe" in the statute contemplated that the benefit of general population control was contemplated. I would guess, it would seem to me you would come up with risk-benefit vis-a-vis that particular patient. I would doubt whether anybody contemplated that you could put on the balance side on the scale the question of the fact that the control of the population is a benefit to that patient in any direct way. I think the rapid growth of the world population is disastrous. But it seems to me, and I raised this question the other day, that when we talk about risk, we are concerned about safety of an individual patient.

You talk about the safety of a particular patient when you talk about risk versus the benefit. I raised the same question with respect to chloramphenicol on which this committee has conducted extensive hearings. Chloramphenicol, when it first came out, was used for a broader spectrum of disease treatment than later, as tetracycline and other drugs came on the market and when all the side effects became known. It is used now only when at least it is known that the disease the patient has is not susceptible to any other drug and the patient's condition is sufficiently serious so that the risk to the patient in not getting the drug is greater than in getting the drug. Then the drug is considered to be "safe."

I think that is what the use of the word "safe" means in the statute. It is a very unsafe drug if you give it to somebody for a headache or a sore throat or an upper respiratory disease, because it is not a drug that treats any of those conditions. It is a very unsafe drug if another drug will treat the disease as effectively but does not have these side effects.

Is that not the way, would that not be your interpretation of what the word "safe" in the statute means?

Dr. HELLMAN. I think you put it very well, and it is quite unlikely that the hearings in 1963 or whenever they were, really considered population as a threat.

Now the climate has changed and, as you and I both know, I would not be here working for the Government if it had not changed. I think that, as Dr. Hertz so well put it, we are having social change. The threat of population growth we need not go into here, but it is real and it is real to each and every individual in this country. And I think you and I both know that.

But let us ignore that. Let us just say, all right, the Congress did not consider that when they were thinking about "safe." They were thinking about safe with alternatives for the individual patient.

Then the argument comes up, do you really have at this moment a satisfactory alternative to these compounds for the number of people you have to treat and the actual conditions for which you are treating them? And I think I would say to you, and this is a judgment statement and not a factual statement, that we really do not.

You can argue about the effectiveness of the diaphragm and you can argue about intrauterine devices, but when you treat the people that I am treating, and these are the economically deprived individuals, you have a problem of quite considerable magnitude over what you can give them that will work for what they want to do.

Senator NELSON. I would remind you of your statement that many of the people you are treating, 55 percent are on the IUD and 40 percent are on the pill.

Dr. HELLMAN. I think that here again, you can not expect a governmental regulatory agency to act as "big brother" to the physicians in the United States. It is well stated, Senator Nelson, by the American College of Obstetricians and Gynecologists—do you have that statement of January 15?

Senator NELSON. No, we have not.

Dr. HELLMAN. I shall leave it for you. It did appear in the press.

This is dated January 15, 1970, a press release by the American College of Obstetricians and Gynecologists. This organization has about 12,000 obstetricians and gynecologists in its membership.

The American College of Obstetricians and Gynecologists considers that the oral contraceptives are accepted therapeutic methods available to the patient under the supervision of her physician. As with any method of therapy the decision to use them should only be made on the basis of a conference between the patient and her doctor. The College deplores inaccurate or sensational reports concerning the scientific data:

This is not the press, these are the doctors they are talking about—

On these drugs.

I think we come right down to the question that a doctor and his patient have to decide when the risks and the benefits are weighed for that individual patient, what she is going to use. And I think that those of us who practice medicine as we believe medicine ought to be practiced, do it in this manner.

Mr. DUFFY. Doctor, may I interrupt you for a second?

Dr. HELLMAN. I am through, really.

Mr. DUFFY. There is a very strong implication in the statement by the College of Obstetricians that you just read that some doctor or some doctors have been popularizing scientific data, or something of that nature. Is that the way you read that statement?

Dr. HELLMAN. You know, you are getting me into a position I do not want to be maneuvered into. I do not want to have to criticize my colleagues. But I think there has been some sensationalism by the medical profession, yes, and it is on both sides of the issue.

Senator MCINTYRE. Would you yield at that point?

Dr. Hellman, I take it from your testimony that you have the feeling of the committee that after this investigation and study, you had to make a decision as to safe and unsafe with regard to this oral contraceptive?

Dr. HELLMAN. The Commissioner would not let us off the hook, that is right.

Senator MCINTYRE. You have also stated in your oral testimony that you personally feel that the yellow light of caution is shining.

Dr. HELLMAN. Yes, sir.

Senator MCINTYRE. Now, in the dilemma that you faced in writing this sentence that has bothered this committee a little bit—that is, "safe within the intent of the legislation"—you had apparently to clear it with legal counsel?

Dr. HELLMAN. Yes, I talked to Mr. Goodrich.

Senator MCINTYRE. Did you, yourself, examine the record of that hearing, the hearing before the Government Operations Committee of the House?

Dr. HELLMAN. Yes, I did.

Senator McINTYRE. I wonder if, when you speak about the intent of the legislation, what you really mean, or the attorneys who assisted you meant, is the interpretation which the FDA has placed on the law and the methods by which it has proceeded to make these benefit-risk decisions? Would that not be a better statement rather than the intent of the legislation?

Dr. HELLMAN. Well, you know, you have me in an area where I cannot even claim to be very knowledgeable. All I can tell you is that Mr. Goodrich said that this was testimony before the Congress and was accepted as a modus operandi for the Food and Drug Administration after that testimony.

Senator McINTYRE. Well, it just seems to me that it might have been more accurate to say that the pill was safe within the interpretation that the FDA had commonly placed upon the legislation.

Just one other comment and question: Since some segments of the news media chose to seize upon the term "safe" without all the qualifications stated in the committee report, do you think in retrospect, Doctor, that it might have been better to avoid the term "safe" or "unsafe" altogether?

Dr. HELLMAN. I would have liked to have avoided the chairmanship of that committee altogether.

Senator McINTYRE. But you were the chairman and you did have to face it. But now in retrospect, do you think it would have been better if, despite the qualifications you put into the committee report, you had done your utmost, even more than you did, to get away from this term "safe" or "unsafe" with regard to this contraceptive?

Dr. HELLMAN. I am afraid that this sentence reflects my personality. I do not like a hedge, and this was a hedge, and the words in there are mine and I am not going to retract them.

Senator McINTYRE. Thank you very much. I have no more questions.

Senator DOLE. Mr. Chairman?

Senator NELSON. Go ahead.

Senator DOLE. Do you see any reason today, Dr. Hellman, to change the wording of this sentence?

Dr. HELLMAN. No; I do not see any reason to change the wording. There will be other reports. The FDA Committee is going to continue to meet. It met yesterday. And Dr. Edwards has indicated that it probably will meet more frequently. I think you can expect an interim report in 6 or 7 months. There is a lot of data that we do not have. We do not have anything on the British data at the present moment.

Senator DOLE. Was there any scientific data that warned of finding the pill was not safe?

Dr. HELLMAN. Any more than in here?

Senator DOLE. Yes.

Dr. HELLMAN. At yesterday's meeting?

Senator DOLE. I mean when you made this finding.

Dr. HELLMAN. I think within that hedge, the sentence expressed what the committee felt.

Senator DOLE. Will you talk about potential hazards. Others say they are not potential, they are very real. Do you consider the hazards potential or real?

Dr. HELLMAN. Well, some of the hazards are real. There is no question about the thromboembolism. And the report does not equivocate there. Some of the other hazards are potential.

Professor Wynn is going to give you some information. But here again, when you come down to the question, has this clinical implication, I think he and I would both agree that we do not have the scientific data necessary to establish this at the present time. That does not mean we are not going to have it.

Senator DOLE. Do you see anything replacing the pill?

Dr. HELLMAN. This is a most difficult question. I do not think that contraceptive research is going to get you an answer the way the Manhattan project got the answer to the atom bomb. It is just not quite that simple and the basic knowledge is not here.

I think that we can expect significant progress if we continue to put money into basic research in adequate amounts. We can get significant progress in the matter of 5 years. But if you are talking about tomorrow or the day after, or next week, I doubt it.

Senator DOLE. During this interim period and as of now, there is no reason not to prescribe the pill?

Dr. HELLMAN. Under the terms the committee wrote, under surveillance and with knowledge by the patient and discussion with the patient, I would say there is no reason not to prescribe the pill.

Senator NELSON. I would not want my question to indicate that I thought the pill was unsafe, under the meaning of the law. I think under the meaning of the law in the current use of drugs and current terms of the law under which we do prescribe drugs, the pill may be safe for some uses. We get into a difficult question, however, where you have a well-motivated person, an educated, middle-class woman who could just as well use another device, who uses the pill solely for convenience—solely for convenience. If convenience is the sole reason for use of the pill, then you get into another area as to whether it is safe under that circumstance.

In the situation that you talked about, a person who is not well motivated, where it would be disastrous to her psychologically or physically to have another baby, then it is probably within the definition of safety. It poses a different kind of safety issue vis-a-vis other prescription drugs; does it not?

Dr. HELLMAN. Yes, it does, and I think, Senator, you and I are saying the same thing. In a discussion with the patient, all of these factors come out plus a lot you have not mentioned.

Senator DOLE. Have you had instances yourself where you have advised against using the pill?

Dr. HELLMAN. Oh, yes, certainly.

Senator DOLE. Any percentage of the number of patients you see?

Dr. HELLMAN. I would think that my private practice is so small that it really does not provide a significant answer. But I think that 55–40 percent ratio of IUD to the pill in our clinic really reflects a desire on the part of the people who work in this clinic to use the pill where it ought to be used.

Senator DOLE. Do you think we are making any progress in determining what risk the patient would incur in using the pill?

Dr. HELLMAN. Well, yes. I think we are making progress in the two areas where we have to make progress; that is, with metabolic effects—the amount of research I do not have data for you on, and I am sorry. It is easy enough to get. But the amount of research

that is going on, on the metabolic effects of these steroids is tremendous.

Senator DOLE. Is there any one type of patient that might incur a greater risk than another?

Dr. HELLMAN. We have all hoped that we could spot the patient. As yet we have no way of doing this.

If you had a patient with an abnormal glucose tolerance curve, meaning she might be a potential diabetic, you would not give her the pill. But this is a difficult task. You cannot do this on eight million people.

Mr. DUFFY. Doctor, may I just clarify something that I believe you said? I do not think you were reading from your prepared statement and I just want to be sure.

Was it your testimony that the scientific data did not warrant the determination that the pill was not safe?

Dr. HELLMAN. Just at the end here, did I say that?

Mr. DUFFY. No, I believe when you were discussing the mechanisms that your committee used in arriving at its conclusions. I think you were at a point where you were saying that you had to come up with a conclusion. Was it your testimony at that point that the data did not warrant determination that the pill was not safe?

Dr. HELLMAN. I think the data did not warrant a flat-footed statement that the pill is unsafe, period, with a recommendation to the Commisisoner that he take it off the market.

Mr. DUFFY. That still remains your conclusion?

Dr. HELLMAN. That is my conclusion, yes, sir.

Senator MCINTYRE. Mr. Chairman.

Doctor, I believe you indicated that the most serious complications of the IUD noted by your committee were associated with the closed circle devices, and the use of such devices has now been largely discontinued. Would you outline for us the risks and dangers associated with the type still in use?

Dr. HELLMAN. We still have the pelvic inflammatory disease problem; that is the inflammation problem. As I indicated to you, packaging is much better than it was and we have no data at the present time that indicates any improvement in this percentage. It is too soon to know whether better packaging has resulted in the diminution of this.

We still have the uterine perforation problem, but I think it is considerably diminished. I would hope that the changes instituted on the basis of the IUD report have made that a safer instrument.

Senator MCINTYRE. Doctor, you say that among countries without laws prohibiting the distribution of contraceptives, only Japan and the U.S.S.R. prohibit distribution or sale of these drugs, oral contraceptives. Do you know the grounds upon which these two countries have refused to allow the use of the pill?

Dr. HELLMAN. No, sir. The reason I smiled is I made a press statement about it once, but I do not think I would want to repeat it.

Senator MCINTYRE. That information, could you——

Dr. HELLMAN. I don't think I have any way of knowing why the Russians did not allow it.

Senator MCINTYRE. Twice you pointed out that the benefits and risks of the pill must be evaluated in comparison with those of other

methods of contraception or no contraception at all. On the benefits side, you have given us two sets of figures concerning the effectiveness of the pill. You say that the theoretical effect of this is reflected in a pregnancy rate of 0.1 per hundred women per year for the combination pill and 0.5 per hundred women per year for the sequentials. However, you say that pregnancy rates reflecting use effectiveness are 0.7 for the combinations and 1.4 for the sequentials. Would you please explain the difference between these two sets of figures and tell us which is more meaningful in attempting to assess the benefits of the pill?

Dr. HELLMAN. I think the use effectiveness. That is the column "All pregnancies" when you should use it. The differences here—in the pill, the reason that there is a difference between theoretical and use effectiveness is the neglect of the patient to take a pill. Apparently—and I say apparently because I do not think we really know—it is more risky to omit one of the sequential pills than it is to omit one of the combination, and this is what gives you the difference.

Senator MCINTYRE. Doctor, you say that the pregnancy rate for the diaphragm is 10 to 30 times higher than for the pill and that the rate for the intrauterine device is 2 to 4 times higher. Would you please tell us whether these comparisons are in relation to the combination or the sequential pills and whether they are based on the theoretical or the use effectiveness rates for the pill?

Dr. HELLMAN. They are based on the use effectiveness. They are based on the combination. They were based, 0.7 to 2.7 and 2.8.

Now, the diaphragm problem is a much more complex one. The table that you are reading from, which is on page 15 of the report, is in there at my insistence, and with some trepidation by my biostatisticians. The reason I say that is that when you talk about use effectiveness you have to specify the population that you are dealing with, and it can vary all over the place, particularly with a method that requires motivation at the time of intercourse. You can have a diaphragm almost as effective—not quite, but almost as effective as the intrauterine devices in a very highly motivated group of people.

Senator NELSON. Would you say 10 times?

Dr. HELLMAN. I think I had a good spread. Did I not say 10 to 30?

Senator MCINTYRE. 10 to 30 times.

Senator NELSON. If I understand your testimony, what you are saying is that the diaphragm does not work if you leave it in your purse. I do not think that is the test of how effective a birth control device is, is it? The pill does not work, either, if you do not take it, does it?

Dr. HELLMAN. That is quite right. But the problem is when you have to use it.

Senator NELSON. Just so the record is clear, you were saying that when properly used, it is not 10 to 30 times less effective?

Dr. HELLMAN. If you are talking theoretical effectiveness and not use of effectiveness, then the condom or diaphragm has a theoretical effectiveness of about 2.6.

Senator MCINTYRE. Did you just give the percentage rates for the diaphragm and the IUD in your answer? Translate those.

Dr. HELLMAN. Let us get straight what we are talking about. If you are talking theoretical effectiveness, the condom and the dia-

phragm have a pregnancy rate of 2.6. The intrauterine devices have a pregnancy rate of 1.9. The sequentials have a pregnancy rate of 0.5, and the combination a pregnancy rate of 0.1.

Senator McINTYRE. Could you tell us where you obtained the pregnancy rate for the pills, the diaphragm, the IUD; how these figures were derived; and how accurate you consider them to be?

Dr. HELLMAN. Dr. Tietze obtained these data from a whole series of reports. I think the references to most of them are in here. A large percentage of them came from the fertility survey conducted by the group at Princeton.

When you ask me how accurate they are, I think you get into the problem that I mentioned to you, that it depends on the population you are using. We hesitate very much to put this sort of thing in tabular data because it does vary with population.

Senator McINTYRE. Thank you very much, Doctor.

Dr. HELLMAN. Are you through with me?

Senator NELSON. Thank you very much, Dr. Hellman. We appreciate your taking the time to come and present your testimony.

Dr. HELLMAN. Senator, can I thank you for the opportunity to be here and for the courtesy and respect with which I have been treated?

Senator NELSON. Thank you.

The next witness is Dr. J. Harold Williams.

Dr. Williams, the committee is very appreciative of your taking the time to come here today. You may present your statement—it will be printed in full in the record and you may deal with it in any way you desire.

STATEMENT OF J. HAROLD WILLIAMS, M.D., LL.B., BERKELEY, CALIF.

Dr. WILLIAMS. Thank you, Senator Nelson, very much. I appreciate the opportunity to appear before this committee on this very important subject.

Senator Nelson and gentlemen of the subcommittee, for almost 20 years I have been a physician, although I have not practiced clinical medicine since about 1960. In that year I was admitted to the California State Bar. I have written several books for the two professions, medicine and law, and I have practiced law most of the time since 1960.

My law practice is devoted almost exclusively to representing patient-plaintiffs in malpractice suits. My chief concern professionally is for justice in all aspects of the doctor-patient relationship. I try to perceive intrusions, from any direction and from any source, into that relationship. Trust and respect, which of course should always be mutual, between doctor and patient is—or should be—the cornerstone of good medical care.

We all recognize that drugs are essential to modern medicine, but the power of the doctor's prescription prerogative sometimes is a serious intrusion into the doctor-patient relationship. Indeed, that power is so awesome that I fear many physicians do not fully comprehend its ramifications when they put pen to pad.

Sometimes the physician is unsuspectingly caught in the middle,

between his conscientious desire to serve his patients and intensive promotional pressure by drug manufacturers. The sad saga of the pill is one of the most phenomenal examples of such an entrapment of our medical profession.

Senator Nelson, you have expressed yourself many times, particularly in your proposed constitutional amendment, about pollution and the wasting of our natural resources. I think here is the proper place to point out that when we talk about the pill being used by 18 million people in the prime of life throughout the world, we are in fact considering an internal pollution, the extent of which is not yet known, but the nature of which is indeed known. And we are threatening the destruction of a large segment of one of our most precious natural resources, the young women of our society. So pollution in this sense is one of the most subtle and, at the same time, one of the most damaging things about the pill. I think this is the context in which we who urge commonsense in this subject should view it.

Senator DOLE. I do not know whether to call you Author Williams, Dr. Williams, or Lawyer Williams.

Dr. WILLIAMS. Anything you would like, Senator.

Senator DOLE. I think it is well to point out that you represent a number of plaintiffs in medical malpractice cases, so you might tend to be somewhat biased in your testimony.

As a doctor, before you, I understand, curtailed your practice in 1960, had you had any personal experience with the pill? Had you had any experience with the pill other than in lawsuits? Outside of trying any cases, have you had any clinical experience with the pill, any research of your own?

Dr. WILLIAMS. No, Senator, I have had no clinical experience with the pill, although since I became interested in the subject I have talked to hundreds of women. I have listened to hundreds of women who have had problems with the pill. I have not done any formal research. My knowledge and my information comes from the literature and talking to people who have had experience with it.

Does that answer your question, sir?

Senator DOLE. Perhaps. I think you have said very forcefully, and I certainly do not want to quarrel with it at this moment, about the sad saga of the pill being one of the most phenomenal examples of such an entrapment. That is a very strong statement, and I assume later on in your statement you may provide some reasons for that statement and provide some powerful evidence.

Dr. WILLIAMS. I will, sir. I have strong feelings on the subject. I admit to my bias. I am biased in favor of the women who are being sold the pill. I am biased in favor of the millions who have dropped out for reasons we do not yet know.

Senator DOLE. How many lawsuits do you have pending now?

Dr. WILLIAMS. I have none pending, Senator. As a result of my choice and my decision to speak out in this fashion, I have withdrawn as counsel in cases involving the pill. I do not now, and I will not in the future, participate as attorney in cases involving the pill.

My interest in the safety of the pill became acute just 14 months ago. At that time, November 1968, I was associated as cocounsel in a lawsuit against a manufacturer of oral contraceptives. As I delved into

the subject of the pill's safety, I was amazed at how much information there was, already in the medical literature, about the dangers and the proof of those dangers being due to oral contraceptives.

By May 1969 the assembled facts and documents, including material not theretofore disclosed to either the medical profession or the public, impelled me to write a book. I hoped it might help alert physicians and the public to the pill's dangers, and it might help avert similar disasters in the future.

One thing I am convinced of as a result of contact with the public this past year—and by the public I mean young people, men and women. I think we should bear in mind that it is not just the women. It is the men who are interested in the welfare of women—they do not want a pill at any price. As much as society wants the pill, they simply are not willing to pay any price. They want to know what the price is.

This, I think, brings the benefit-risk ratio talk into focus. Whenever we think of benefits and risks, we also, I think, have to talk about damage. It is one thing to face a risk; it is another to experience the harm that that risk, or the risk of whatever might happen, in fact has happened. And this damage is in terms of health, life, and enormous amounts of money.

So, looking at benefits and risks only, I think it is being shortsighted and I urge you to consider the cost and these other factors.

I think it is important also that we ponder what the cost is going to be as long as these deliberations and indecisions and indefinite answers persist. If we allow another 10 years to go on, what is the additional cost going to be? That, gentlemen, I think, is the most crucial question to be grappled with here.

As I point out some of the things that have happened in the advertising and promotion of the pill, please bear in mind that the average practicing physician relies upon the drug companies for much, if not all, of his information about drugs. He may read some of the articles in medical journals which report adverse reactions to certain drugs, but by and large he does not have time, nor is he motivated, to read all journals, to sift the poor articles from the good, and to correlate all the information.

Obviously, he cannot repeat the research that has been done on drugs in his own practice. Usually he looks to the most convenient central source of information, the Physicians Desk Reference, a compendium of drug company advertising. Most of us here in this room, I think, understand that the PDR is no more than a compendium of drug company advertising. The doctor assumes that the drug companies are honest and that the FDA has been a vigilant watchdog to protect him and his patients. This is true sometimes; sometimes it is not.

For the purpose of convenience in this discussion, I will use the word advertising in reference to graphic presentations to physicians which are readily identifiable as commercially sponsored sales messages.

By promotion I mean all other communications aimed at promoting the sales, use, and acceptance of the pill by the medical profession and the public. Advertising of the pill to the medical profession has been characterized by many statements that tend to be misleading. If in

fact they are not grossly, overtly misleading. Morton Mintz has pointed out in his book—not pointed out, he has given specific examples of where companies were actually caught misleading the physicians to whom advertising had gone. It is very interesting how these companies—Ortho, Syntex, Mead-Johnson—were forced to send out remedial letters: February 1, 1967; January 22, 1968—confessing, under pressure, of course, to the doctors that some of their advertising claims have been misleading.

But there are other examples. In Enovid Bulletin No. 20, published in 1964, under a section headlined "The responsibility of leadership" is this statement:

* * * few drugs in any category have ever been subjected to clinical tests as exhaustive as those already undergone by Enovid.

The reader was expected, no doubt, to understand that statement as applying to safety as well as to efficacy. I think much of the testimony that has been heard before this committee in the last 2 weeks underscores the fact that research as to safety has been a long time in coming and that it had not been exhaustive by 1964 and certainly has not been exhaustive even today.

In that same bulletin, we find:

In the mass of data now on hand, there is *no* evidence—the italic is mine—that long-term inhibitation of ovulation with Enovid impairs post-treatment fertility, * * *

Again, a statement implying that exhaustive work relevant to the subject had been done when it had not.

Ambiguous language has been employed many times to take away the sting from information which should have had a warning impact on the physician. For example, in Physicians' Product Brochure No. 62, printed March 16, 1964:

There is no direct evidence that Enovid alters the diabetic state. However, in a few instances some degree of difficulty in the management of diabetic patients has been reported in connection with Enovid therapy * * * They may be expected to return to their pretreatment manageability on discontinuance of the drug.

It does not alter the diabetic state but they return to their pretreatment manageability on continuance of the drug.

Senator McIntyre (presiding). Excuse me for interrupting, but on page 3 you have already mentioned Enovid Bulletin No. 20 and the other, Physicians' Product Brochure No. 62. Would it be possible for you to submit these to the committee? You can make them available to the transcriber.

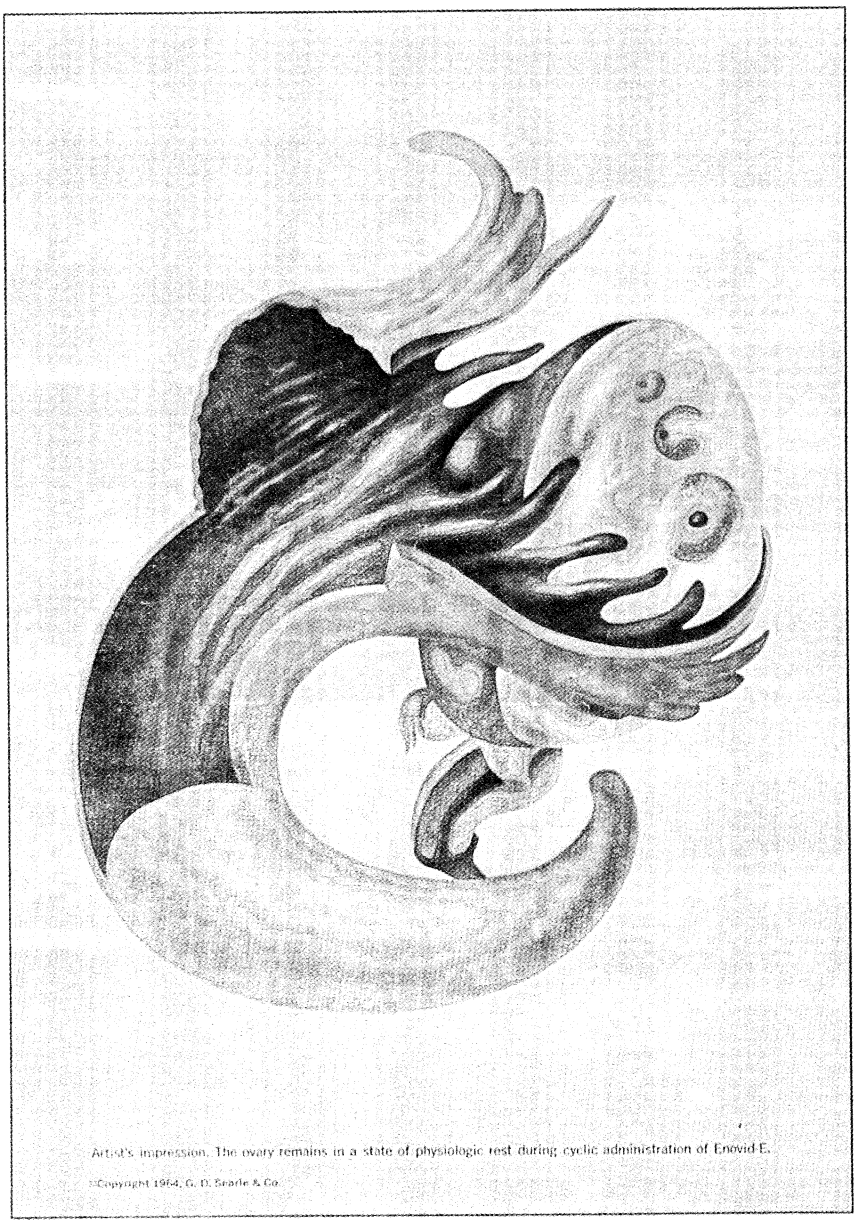
Dr. Williams. Certainly, Senator. I have them right here.

(The documents referred to follow:)

ENOVID® BULLETIN NO. 20

May 1964 / Experience behind Enovid-E®—new, low-dosage form of "The Pill"

. . . *unfettered* From the beginning, woman has been a vassal to the temporal demands—and frequently the aberrations—of the cyclic mechanism of her reproductive system. Now, to a degree heretofore unknown, she is permitted normalization, enhancement or suspension of cyclic function and procreative potential. This new medical control is symbolized in an illustration borrowed from ancient Greek mythology—Andromeda freed from her chains.



Artist's impression. The ovary remains in a state of physiologic rest during cyclic administration of Enovid-E.

Experience Behind Enovid-E®— New, Low-Dosage Form of "The Pill"

Each tablet of ENOVID-E contains:

norethynodrel	2.5 mg.
mestranol	0.1 mg.

ENOVID-E should not be confused with other dosage forms of ENOVID:

	5-mg. tablet*	*10-mg.* tablet*
norethynodrel	5.0 mg.	9.85 mg.
mestranol	0.075 mg.	0.15 mg.

*Note that one-half of a 5-mg. tablet or one-fourth of a 10-mg. tablet cannot be substituted for ENOVID-E.

The responsibility of leadership. "In the last eight years oral contraception has become a reality, and this undoubtedly represents as great a medical landmark as the introduction of antibiotics."[1]

ENOVID opened the era of oral contraception and "has led the field."[2] Because of its worldwide impact, those associated with the development of ENOVID have long felt a responsibility to study this drug and its effects with a thoroughness and persistence that are almost unprecedented. As a result, few drugs in any category[3] have ever been subjected to clinical tests as exhaustive as those already undergone by ENOVID. And there is no question that ENOVID is "the most thoroughly studied synthetic progestogen."[4]

After 35,000,000 cycles, the consensus. Intensive exploration of the organic and physiologic effects of ENOVID, during and after longer and longer periods of administration, is slated to continue indefinitely. But certainly the voluminous evidence produced by almost a decade of clinical study, together with experience in more than 6,100,000 women for more than 35,000,000 cycles, permits these conclusions:

- The response to prolonged use of ENOVID appears to be remarkably similar to the response to the natural ovarian hormones. In the mass of data now on hand, there is no evidence that long-term inhibition of ovulation with ENOVID impairs post-treatment fertility, harms subsequent children, delays or extends the menopause, or results in thyroid, adrenal or pituitary dysfunction.
- Experience indicates that endocrine function typical for the individual patient prior to use of ENOVID returns promptly after it has been discontinued.
- There is no doubt that ENOVID is virtually 100 per cent effective for extended suspension of fertility.

The lowest contraceptive dose with more than five years of confirmation. While certain phases of ENOVID research will require continuing study for many years to come, one important phase was brought to a successful conclusion earlier this year: the determination and clinical confirmation that 2.5 mg. of norethynodrel will afford the contraceptive effectiveness assured by the 5-mg. and 10-mg. tablets of ENOVID. The introduction of ENOVID-E—2.5 mg. of norethynodrel and 0.1 mg. of mestranol—represents the culmination of this study.

In the initial clinical tests of ENOVID for conception control, the 10-mg. tablet was employed. It was soon determined that a tablet containing half the ingredients in the original 10-mg. tablet was equally effective in preventing ovulation and conception. Clinical trials of a 2.5-mg. tablet were initiated[5] in August 1958, in Puerto Rico, where the original ENOVID study[6] had begun more than two years earlier. These were the first tests of a low-dose oral contraceptive.

A tablet offering half the contents of the 5-mg. tablet was shown[7] to have insufficient mestranol for original support of the endometrium. But the 2.5-mg. dose of norethynodrel proved successful when combined with 0.1 mg. of mestranol. (The marked lowering of the norethynodrel-to-mestranol ratio in the 2.5-mg. tablet should be noted, since it means that one-fourth of the 10-mg. tablet or one-half of the 5-mg. tablet *cannot* be substitued for the combination now available as ENOVID-E.)

By the end of 1959, clinical evaluation of the 2.5-mg. tablet was in progress in the continental United States and other countries as well as Puerto Rico. The expanded clinical test program included a variety of ethnic groups in clinic and private practice. By September of 1963, 2,946 women had already participated in ENOVID-E trials for from 1 to 46 cycles, for a total of 33,416 cycles. (See Tables 1 and 2.)

In no instance in any of the clinical trials[5,6,8,10-28]

TABLE 1. Clinical studies of ENOVID-E. Summary of 2,946 cases by cycles.

CLINICAL GROUPS	CYCLES COMPLETED						
	1st-5th	6th-11th	12th-17th	18th-23rd	24th-29th	30th-36th	Over
Wiseman[8] (Slough, England)	782	364	241	134	56	12	7
Binks, Cambourn and Papworth[9] (Australia)	64	47	23	18	13	11	9
Wisdom[10] (London)	235	209	182	123	47	2	–
Chinnatamby[11] (Ceylon)	673	139	48	–	–	–	–
Satterthwaite[12] (Humacao, P.R.)	94	75	55	41	30	12	10
Comparative Study[13]	198	164	112	78	31	–	–
Tyler[14] (Los Angeles)	106	101	83	73	35	4	3
García and Pincus[15]* (San Juan, P.R.)	413	291	204	168	102	56	48
Flowers[16] (Chapel Hill, N.C.)	245	214	130	76	37	1	–
Burket[17] (Cincinnati, Ohio)	136	113	95	37	11	–	–
	2,946	1,717	1,173	748	362	98	77

The above tabulation shows that "approximately 362" women were in the third year or more of medication with Enovid-E.
*In this study 234 women received other dosage forms of Enovid before taking Enovid-E for from one to fifty-six cycles and 118 of this group were in their fourth year or more of medication with Enovid and Enovid-E at the end of April 1963.

did pregnancy occur while ENOVID-E was taken cyclically as directed. It is clear, as Pincus[24] has written, that ". . . control at the lowest dosage employed (2.5 mg./day) is just as effective as at the highest dosage (10-mg./day). We have several times pointed out that with faithful following of the medication regimen, contraceptive efficiency is practically 100 per cent. In more dramatic terms, Andrews and Andrews[18] declare that the contraceptive effectiveness of ENOVID-E, like that of ENOVID, "apparently exceeds that of any other available method short of abstinence or surgical extirpation of the pelvic organs."

The absence of after-effects — functional or organic. With ENOVID-E, as with the higher doses of ENOVID, the woman's normal or pretreatment physiologic status returns promptly when cyclic administration is discontinued.

The resumption of ovulation and menstruation and the full restoration of fertility[3,18,21,23,28-34] have been demonstrated time and again after cyclic use of ENOVID-E or ENOVID, even when ovulation has been suppressed for several years. Pullen[23] found that "ovulation and fertility appeared to be unimpaired" when women stopped taking ENOVID-E. Andrews and Andrews[18] reported a "prompt return of ovulation usually in the first cycle, always in the second," and noted "no diminution of fertility" after therapy.

Satterthwaite[28] has reported on post-treatment fertility in 96 women who took ENOVID-E or ENOVID for from 12 or more cycles: One month after medication was stopped, 43 (44.7 per cent) were pregnant; after an additional four months, 79 (82.2 per cent) were pregnant. "All but four of the remaining seventeen women were known to have used contraceptive methods or to have been separated [from their husbands] part of the time." In this same study, follow-up of 256 women who remained at risk of pregnancy after use of ENOVID-E or ENOVID revealed that 253 had become pregnant. These findings are supported by those of Pincus[21] in 174 women who took ENOVID-E or ENOVID for 1 to 40 cycles.

Perhaps even more significant is the fact that a prompt return of normal physiologic function has been demonstrated[31,35] in women with endo-

TABLE 2.
Total cycles of clinical experience with ENOVID.

(as of May 1964)

CLINICAL GROUP	CYCLES OF USE
Wiseman[9]	6,299
Binks, Cambourn, and Papworth[9]	843
Wisdom[10]	3,967
Chinnatamby[11]	3,453
Satterthwaite	
Humacao[12]	1,525
Comparative[13]	2,443
Tyler[14]	2,092
García and Pincus[15]	6,138
Flowers[16]	2,975
Burket[17]	1,841
Andrews and Andrews[18]	521
Mears[19]	181
Mears[20]	1,288
	33,506

metriosis treated daily with 12 to 28 times the norethynodrel dose contained in ENOVID-E.

These massive doses were given every day—not cyclically—for nine to twelve months. After this treatment, the women whose courses were followed either by measurement of basal body temperature or by endometrial biopsy gave evidence of spontaneous ovulation within six to eight weeks.

It is generally accepted that ENOVID-E and ENOVID inhibit ovulation by reducing pituitary gonadotropin secretion. The prompt resumption of ovulation when medication is suspended indicates that gonadotropin inhibition is entirely reversible — that prolonged administration of ENOVID-E or ENOVID has no discernible effect on post-treatment pituitary function. There is no contrary evidence. There are no reports of any serious toxic manifestations involving the pituitary or any other endocrine organ as a result of ENOVID or ENOVID-E administration. Again, observations during and after cyclic use of these agents are supported by experience with the continuous administration of high doses in patients with endometriosis. In these women, too, there is an apparent resumption of normal gonadotropin function[31] after ENOVID therapy.

Commenting on long-term inhibition of the anterior pituitary, Parkes[36] reminds us that "the ovulation-producing activity of the human pituitary gland is inhibited for a year or more during pregnancy and lactation; so in this respect the continued use of the pill may be likened to a rapid succession of pregnancies. However undesirable in other ways, a succession of pregnancies is not usually regarded as . . . endocrinologically catastrophic."

Ovarian biopsies revealed no deleterious effects after prolonged cyclic administration of higher doses than those received by women taking ENOVID-E. Actual counts were made of the number of primordial follicles in the ovaries of ENOVID-treated women and normal, untreated women. Among the women in the study[5] were some who had received ENOVID for as long as twenty cycles. García and Pincus[25] consider these follicle counts "reassuring in that the follicle population density is not significantly different from the normal control counts for the respective age groups."

Cytologic studies of the vagina and endometrial biopsies have also revealed[32] no harmful effects after larger contraceptive doses than those afforded by ENOVID-E. Once more, the confirmatory findings in women treated for endometriosis are particularly interesting; endometrial biopsies and subsequent pregnancies in these women offer no evidence[31] that the endometrium has been functionally compromised by high doses of ENOVID administered daily for months.

In reviewing the responses to prolonged ENOVID-E or ENOVID therapy, Pincus[21] reported: "No significant change in the incidence of irregularities of the breasts, abdomen, fundus, vaults and adnexae, introitus, or in the proportion of palpable ovaries occurs either in relation to the duration of medication or in comparison with control subjects."

The suggestion that oral contraceptives may delay the menopause has been dismissed by Flowers[37] with the comment that "we have not found the fountain of youth." There is no evidence that the suspension of ovulation during frequent

pregnancies or by cyclic administration of ENOVID-E or ENOVID delays the onset of the menopause or prolongs it. In patients taking ENOVID cyclically, as in the grand multipara, there is no reason to doubt that the natural aging process, with eventual total suppression of ovulation and replacement of primordial follicles with fibrosis, proceeds at its normal pace. It should be noted that when ENOVID is given cyclically to a woman approaching, or already in, the menopause, she may be expected to respond with regular cycles. It is necessary to discontinue ENOVID to determine whether spontaneous ovulation and menstruation have ceased in a menopausal woman.

Whenever a progestin is prescribed for long periods, the question of possible androgenic effect is of importance. It is worth recalling that one reason ENOVID was chosen to be tested as the first oral contraceptive[2] was that "it is neither androgenic nor antiestrogenic." Kistner[38], in a review of progestational steroids, notes that while the antiestrogenic activity of norethindrone is about nine times greater than that of progesterone, "Norethynodrel actually is estrogenic, having 3 to 7 per cent of the estrogenic activity of estrone. . . ." In a recent discussion of oral contraception, Jackson[26] stressed "the essential clinical oestrogenicity of products containing norethynodrel" as opposed to the "heavy overlay of progestogenic and even of mild androgenic activity" with norethisterone tablets. In view of this, it is not surprising that the author[39] of the one report of fetal masculinization associated with ENOVID administration later declared that the occurrence was probably coincidental.

It is apparent that with ENOVID-E, as with ENOVID, when cyclic use is discontinued, the effects on reproductive organs and on the pituitary are rapidly reversed; there is no harm to subsequent children, and no delay or extension of the menopause. As to fertility, there is no evidence that it is in any way impaired in women who have used ENOVID-E or other oral contraceptives. Instead, as it is pointed out[40] in the *British Medical Journal*, "there is some evidence that it might be increased."

Factors enhancing acceptance: A paucity of complaints. "Acceptability is the most critical factor in the effectiveness of a contraceptive method."[41]

A woman's acceptance of an oral contraceptive is, of course, heavily influenced by the incidence and severity of side effects. Physicians familiar with ENOVID-E agree that the relatively few side effects encountered are for the most part mild and transient. Naturally, there are differences in the incidences of the various side effects reported by different investigators. But every study shows that after the first cycle, as medication is continued, there is a sharp decline in the incidence and severity of virtually every type of complaint. After the third cycle of therapy the incidence of side effects is very low.

Indeed, one investigator[16] with long experience in the study of oral contraceptives has said: "The decrease in the incidence of side effects to practically nil after the third cycle of medication in this group is remarkable."

The short duration of the nausea that is sometimes encountered is indicated in the accompanying graph. Pullen's comment[23] is typical: "Whatever the degree, as estimated by the patient, it had cleared considerably by the second cycle, and all were free of it by the fourth cycle." In the experience of Andrews and Andrews[18] with ENOVID-E, nausea is "seldom significant," and "has rarely been encountered after the first cycle."

Nausea during the initial cycles of ENOVID-E administration is believed to be another manifestation of the pseudopregnancy produced by ENOVID-E. It has been suggested that women who have experienced nausea during pregnancy are more likely to have some degree of nausea during the initial cycles of ENOVID-E medication. If nausea occurs—or seems likely to occur—it can often be controlled by taking the tablet with meals or with a glass of milk at bedtime, or by prescribing an antacid or antinauseant with the ENOVID-E tablet during the first two or three cycles.

The pattern for breakthrough bleeding is similar to that occurring with nausea. Like the other investigators, Binks, Cambourn and Papworth[9] found that the incidence of breakthrough bleeding "was highest in the first cycle, and dropped during the succeeding two cycles." Spotting and breakthrough bleeding are usually controlled by increasing the daily dosage of ENOVID-E. The in-

creased dosage may be required for four or five days, after which the original schedule may be resumed. Mears[19] points out, "There is no reason to suppose that this breakthrough bleeding is harmful in any way. . . ." The occurrence of spotting does not mean that ENOVID-E has failed to control ovulation.

Just as "silent menstruation" (an amenorrheic cycle) is encountered on rare occasions in women who are not taking oral contraceptives, withdrawal bleeding may fail to occur after a cycle of medication with ENOVID-E. There is nothing serious about this rare phenomenon. But it is a possibility each woman should know when she begins to take ENOVID-E. Even in the absence of withdrawal bleeding, ovulation may occur during the subsequent cycle—perhaps earlier than usual—if tablet taking is not resumed within seven days after the last tablet of the preceding cycle. Even in the event that pregnancy has occurred, due to missed tablets, ENOVID may be continued with safety. Its effect on the pregnancy would be supportive.

Weight change during cyclic use of ENOVID-E has not been a problem. It has been found[24] that "overall reports of weight gain tend to balance those of weight loss." For example, of 289 women[13-15] in three recent studies, one out of six neither gained nor lost weight, and the number of women who gained weight was approximately equal to the number who lost weight. The change in either direction was not excessive, and occurred for the most part during the early cycles of medication.

No consistent effect on libido has been detected with ENOVID-E or ENOVID. In his extensive experience with ENOVID and ENOVID-E, Pincus[24] has found: "About 80 per cent report no change, 5 per cent to 8 per cent an increase and 13 per cent to 18 per cent a decrease. The extent to which modesty governs these answers is, of course, imponderable, but certainly no drastic change is indicated."

Factors enhancing acceptance: Gynecologic benefits. Investigators[40] have found that often during cyclic use of ENOVID-E women are relieved of what have been termed the "naturally occurring 'side effects' of the menstrual cycle."

Andrews and Andrews[18] report that in many women taking ENOVID-E or ENOVID cyclically, there is a reduction in the volume of menstrual flow, "and this has been of help in those having menorrhagia." In addition, "Relief of premenstrual tension has been frequently noted," and "Dysmenorrhea has been eliminated or significantly improved in 87.5% of patients where this has been present." In Pullen's series[23] "Of the 59 patients who complained of dysmenorrhoea before entering the trial . . . 67% had a decrease in pain" during cyclic use of ENOVID-E.

Factors enhancing acceptance: Additional benefits. As Mears[19] points out: "The real indication of acceptability to the patient . . . is presumably whether she perseveres with this method. . . ."

Women have shown remarkable perseverance in the use of ENOVID-E and also great enthusiasm. Pullen[23] states that her patients "were strongly in favour of oral contraception once they had used this method of birth control." According to Binks and his colleagues[9] in their report on experience with ENOVID-E and ENOVID: "The majority of women taking part in the trial state that they hope it will not be necessary to return to the more conventional methods of contraception at the completion of the trial; this attitude generally confirms our impression that this method of fertility control is acceptable to most women, and that troublesome side effects are of low incidence after the first two or three cycles."

The reasons for this remarkable acceptance of ENOVID-E and ENOVID are not hard to find. As Pullen[23] has pointed out, "The minor disadvantages of oral contraceptives can readily be shown by tables. The contribution they make to human happiness does not lend itself to statistical analysis." The "contribution to happiness" is apparent in the reports of many investigators.

Elaborating on the fact that "The general acceptance by women of this regimen has been excellent," Andrews and Andrews[18] note: "Many have commented on a feeling of well-being and freedom from fear of pregnancy. The aesthetic value of being freed from the intrusion of mechanical contraceptive devices has been mentioned by many." In the same vein, Pullen[23]

writes, "The overall effect . . . was that the patients felt an increase in well-being and marital happiness. The effects were not limited to the wives. Many husbands expressed their satisfaction with the method and none wished to return to methods formerly used." Mears, too, thinks[19] that much more prominence should be given to the positive effects mentioned by patients: "Many patients have expressed themselves as being absolutely delighted with the freedom from contraceptive measures related to coital acts, of being more confident and relaxed at intercourse . . . feeling better than ever before. . . ." Physicians as well as their patients, it is stated[40] in the *British Medical Journal*, "find great relief in the freedom from anxiety which this method [oral contraception] offers."

These psychologic aspects of oral contraception are no doubt largely responsible for the fact that ENOVID-E and ENOVID have attained a remarkable acceptance and rapid popularity[2] "no matter what the intellectual or social status of the women may be." Commenting on the acceptance of the oral method, it is stated[40] in the *British Medical Journal:* "Though it was at first expected that this method would be suitable only for intelligent conscientious women, this is not so. It has been found that many feckless women who have been quite inconsistent over other contraceptive measures have found this method highly acceptable and have never missed a tablet."

Summary: The significance of Enovid-E. Clinical experience — the longest experience behind any low-dosage oral contraceptive — makes it clear that ENOVID-E enjoys outstanding acceptance, psychologically as well as physically, and that its effects, like those of ENOVID, are fully reversible when cyclic use is terminated.

Acceptance is further enhanced by a very significant practical consequence of the low ENOVID-E dosage: economy. Women may now have the benefits of fully effective oral control of fertility at far less expense.

References

1. Goldzieher, J. W.: Newer Drugs in Oral Contraception, Med. Clin. N. Amer. *48*:529-545 (March) 1964.
2. Garcfa, C.-R., and Pincus, G.: Hormonal Inhibition of Ovulation, in Calderone, M. S. (editor): Manual of Contraceptive Practice, Baltimore, The Williams & Wilkins Company, 1964, pp. 206-221.
3. Swyer, G. I. M.: Notes and Queries: Oral Contraceptives, Practitioner *190*:155-156 (Jan.) 1963.
4. Roland, M.; Clyman, M. J.; Decker, A., and Ober, W. B.: Classification of Endometrial Response to Synthetic Progestogen-Estrogen Compounds, Fertil. Steril. *15*:143-163 (March-April) 1964.
5. Garcfa, C.-R.; Rock, J., and Pincus, G.: Proceedings of a Symposium on Enovid: Observations on Prolonged Administration of Enovid, Chicago, Searle Research Laboratories, 1959, pp. 35-41.
6. Rice-Wray, E.: Proceedings of a Symposium on 19-Nor Progestational Steroids: Field Study with Enovid as a Contraceptive Agent, Chicago, Searle Research Laboratories, 1957, pp. 78-85.
7. Eckstein, P., and others: The Birmingham Oral Contraceptive Trial, Brit. J. Med. *2*:1172-1179 (Nov. 4) 1961.
8. Wiseman, A.: Investigator's Clinical Report, April 15, 1963; this is a continuation of the published report, Reference No. 19.
9. Binks, R.; Cambourn, P., and Papworth, R. A.: Preliminary Report of a Clinical Trial of Oral Norethynodrel for Fertility Control, Med. J. Australia *1*:716-717 (May 12) 1962.
10. Wisdom, C.: Investigator's Clinical Report, Dec. 23, 1963.
11. Chinnatamby, S.: Clinical Trial of Oral Contraceptives, Annual Report, Family Planning Association of Ceylon, Colombo, 1963, pp. 23-26.
12. Satterthwaite, A. P.: Investigator's Clinical Report, April 30, 1963.
13. Satterthwaite, A. P.: Investigator's Clinical Report, May 10, 1963.
14. Tyler, E. T.: Investigator's Clinical Report, March 31, 1963.
15. Garcfa, C.-R., and Pincus, G.: Investigators' Clinical Report, April 30, 1963.
16. Flowers, C. E.: Investigator's Clinical Report, June 27, 1963.
17. Burket, R.: Investigator's Clinical Report, July 30, 1963.
18. Andrews, W. C., and Andrews, M. C.: The Use of Progestins for Oral Contraception, Southern Med. J. *55*:454-456 (May) 1962.
19. Mears, E.: Clinical Trials of Oral Contraceptives, Brit. Med. J. *2*:1179-1183 (Nov. 4) 1961.
20. Mears, E.: A Comparative Study of Three Available Oral Contraceptives (Proceedings of the Society for the Study of Fertility, Annual Conference, June 27-30, 1962), J. Reprod. Fertil. *4*:229-230 (Oct.) 1962.
21. Pincus, G., Suppression of Ovulation with Reference to Oral Contraceptives, in Gardiner-Hill, H. (editor): Modern Trends in Endocrinology 2nd series, London, Butterworth & Co. (Publishers), Ltd., 1961, pp. 231-245.
22. Jackson, M. H.: Observations on the Use of Certain Orally Active Progestogens for the Control of Fertility in Women, Proc. Roy. Soc. Med. *54*:16-19 (Nov.) 1961.
23. Pullen, D.: "Conovid-E" as an Oral Contraceptive, Brit. Med. J. *2*:1016-1019 (Oct. 20) 1962.
24. Pincus, G., Control of Reproduction in Mammals, in Wolstenholme, G. (editor): Man and His Future, Boston, Little, Brown & Co., 1963, pp. 79-90.
25. Garcfa, C.-R., and Pincus, G.: Ovulation Inhibition by Progestin-Estrogen Combination, presented at the International Fertility Association Meeting in Brussels, Belgium, March 2-3, 1963, in press.
26. Jackson, M. C. N.: Oral Contraception in Practice (The Sixth Oliver Bird Lecture), J. Reprod. Fertil. *6*:153-173 (Aug.) 1963.
27. Satterthwaite, A. P., and Gamble, C. J.: Conception Control with Norethynodrel: Progress Report of a Four-Year Field Study at Humacao, Puerto Rico, J. Amer. Med. Wom. Ass. *17*:797-802 (Oct.) 1962.
28. Satterthwaite, A. P.: Control of Ovulation with Norethynodrel; Progress Report of a Five-Year Field Study at Humacao, Puerto Rico, presented at the Fourth World Congress on Fertility in Rio de Janeiro, Aug. 8-15, 1962, in press.
29. Guttmacher, A. F.: Oral Contraception, Postgrad. Med. *32*:552-558 (Dec.) 1962.
30. Garcfa, C.-R.: Symposium: Newer Developments in the Treatment of Menstrual Dysfunctions in Office Practice: Long-Term Experience, report presented at Jefferson Medical College, Philadelphia, April 27, 1963.
31. Kistner, R. W.: Infertility with Endometriosis: A Plan of Therapy, Fertil. Steril. *13*:237-245 (May-June) 1962.
32. Tyler, E. T.: Oral Contraception, J.A.M.A. *175*:225-226 (Jan. 21) 1961.
33. Council on Drugs: New Drugs and Developments in Therapeutics: Norethynodrel with Mestranol (Enovid), J.A.M.A. *183*:949-951 (March 16) 1963.
34. Rock, J.: Population Growth (Editorial), J.A.M.A. *177*:58-60 (July 8) 1961.
35. Kistner, R. W.: The Use of Steroidal Substances in Endometriosis, Clin. Pharmacol. Ther. *1*:525-537 (July-Aug.) 1960.
36. Parkes, A. S.: Change and Control in Human Populations, Lancet *1*:341-344 (Feb. 16) 1963.
37. Flowers, C. E., in Goldfarb, A. F.: Ovulation Control, Med. Sci. *14*:42-47 (Nov.) 1963.
38. Kistner, R. W.: Steroid Compounds with Progestational Activity, Postgrad. Med. *35*:225-232 (March) 1964.
39. Grumbach, M. M.: Some Aspects of the Pathogenesis of Anomalies of Sex in Man, Pacific Coast Fertility Society, Las Vegas, Nev., Nov. 12, 1960.
40. Today's Drugs: Oral Contraceptives, Brit. Med. J. *2*:550-551 (Aug. 31) 1963.
41. Calderone, M. S., Three Contraceptive Axioms, in Calderone, M. S. (editor): Manual of Contraceptive Practice, Baltimore, The Williams & Wilkins Company, 1964, pp. 151-153.

Summary of prescribing information

Functional Uterine Bleeding

Recommended Treatment. For emergency control of severe bleeding in menorrhagia or metrorrhagia, 20 to 30 mg. of ENOVID should be given until the bleeding is controlled. Usually the daily dose may then be reduced to 10 mg. daily and continued through day 24 of the cycle. The drug is then discontinued and the patient will usually menstruate approximately three days later.

Following treatment of this initial cycle the patient should be given 5 to 10 mg. of ENOVID daily from day 5 through day 24 of the next two or three cycles.

Ovulation Control

ENOVID has been shown in extensive studies to be extremely effective in inhibiting ovulation. For additional information the physician is referred to The Physicians' Product Brochures: *Enovid-E for Contraception,* No. 62, and *Enovid,* No. 67, which are available from G. D. Searle & Co. upon request.

Recommended Treatment. ENOVID-E or one 5-mg. ENOVID tablet should be prescribed daily for twenty days beginning on day 5 of the cycle, counting the first day of menstruation as day 1. Patients so treated will usually menstruate on day 28.

Dysmenorrhea

Patients with primary dysmenorrhea usually are relieved by inhibiting ovulation.

Recommended Treatment. A daily dose of 5 mg. should be given from day 5 of the cycle through day 24. The drug is then discontinued and the patient will usually menstruate approximately three days later. Two or three additional cycles are treated in the same manner and therapy interrupted to determine the need for further treatment.

Premenstrual Tension

Although ENOVID may be used for the treatment of premenstrual tension and may prove successful, an aggravation of premenstrual tension occurs occasionally, presumably as a result of sodium retention.

Recommended Treatment. The dose of ENOVID is 5 mg. daily from day 5 through day 24. The treatment should be repeated for three consecutive cycles.

Primary and Secondary Amenorrhea

If no physical cause for amenorrhea is found, it is possible to provide regular withdrawal bleeding closely resembling a normal menstrual period with ENOVID therapy. In both types of amenorrhea, it is known that a course of ENOVID treatment may be followed by resumption of normal menstruation.

Recommended Treatment. One 5-mg. tablet of ENOVID should be given daily for ten days to establish a cycle, and then 5 mg. daily from day 5 through day 24 for two consecutive cycles. Dosage should be increased for a few days if breakthrough bleeding occurs. The drug should be omitted after the third cyclic course to determine the need for further therapy.

Idiopathic Infertility

It has been suggested that infertile women with no detectable abnormality may be subject to endometrial hypoplasia with consequent dysfunction of the uterus or tubes. ENOVID may be prescribed in order to stimulate endometrial development in the natural sequence.

Recommended Treatment. One 5-mg. tablet of ENOVID is administered daily from day 5 for twenty days. If breakthrough bleeding occurs, the dosage should be repeated for three consecutive cycles. Conception should then be attempted in the immediate following cycles, around the expected time of ovulation. Ovulation in the first cycle after treatment may be delayed for three to five days or even longer; subsequent cycles will usually revert to the duration previously typical for the individual patient.

Endometriosis

Recommended Treatment. A daily dose of ENOVID should be given for six to nine months or more on the following schedule: 5 mg. should be given for two weeks beginning on day 5 of a menstrual cycle. This daily dose should be given continuously without cyclic interruption and increased 5 mg. every two weeks until the patient is receiving 20 mg. daily. This daily dose of 20 mg. should be continued for six to nine months and should be further increased (up to 40 mg. daily) if breakthrough bleeding occurs.

Therapy may be discontinued if the disease is mild and the lesions are no longer palpable after six months. When the condition is more severe it will be necessary to continue treatment for nine months longer.

Recurrent and Threatened Abortion

ENOVID results in endometrial changes which closely mimic the normal endometrium of pregnancy and has been well demonstrated to maintain the integrity of the endometrium over prolonged periods. It should be borne in mind that in threatened abortion the first signs are frequently late in the actual condition. For this reason, the re-establishment of endometrial integrity may be very difficult or impossible by the application of any known method.

Recommended Treatment. Recurrent Abortion. A daily dosage of 20 mg. of ENOVID is started as soon as pregnancy is suspected. If the gonadotropin pregnancy test is positive the dosage should be continued to term or at least until the end of the fifth month of pregnancy. If spotting occurs during pregnancy this dosage may be increased to 40 to 50 mg. daily until the bleeding stops.

Threatened Abortion. Treatment must be started before the abortion has reached an advanced stage. From 20 to 30 mg. daily is given for seven to ten days and then 10 to 20 mg. daily until term. If the symptoms of impending abortion reappear the dosage should be increased immediately until the symptoms disappear.

Infertility Due to Inadequate Luteal Phase

Recommended Treatment. Three days after ovulation 5 mg. of ENOVID is given daily and continued through at least five months of the pregnancy if a gonadotropin test reveals that the patient is pregnant. If the test is negative, ENOVID should be discontinued and similar therapy employed in a subsequent cycle.

Adjustment of the Menses

Recommended Treatment. To *postpone* the menses 10 mg. of ENOVID should be given daily, beginning at any time up to a week before the expected menstruation. This dose will delay menstruation for periods up to two weeks; for longer delays the daily dose should be increased to 20 mg. The drug may be discontinued at any desired time, and the menstrual flow may be expected about three days later.

To advance the onset of menstrual flow 5 mg. of ENOVID should be given daily beginning on day 5 of the cycle. A ten-day course should be used and the drug discontinued. The menstrual flow should be expected about three days later. With this therapy the anticipated menstrual flow may be advanced ten days in a twenty-eight-day cycle.

Test for Pregnancy

The administration of ENOVID to a patient who is pregnant will provide endometrial support which is only additional to her endogenous hormones. On the other hand, the discontinuance of ENOVID in a patient who is not pregnant will withdraw her sole endometrial support and a bleeding episode will result. This use of the drug makes it possible to distinguish between amenorrhea due to pregnancy and that due to other causes.

Recommended Use. In this use, it is recommended that 10 mg. of ENOVID be given daily for four days. A positive finding is made if withdrawal bleeding does not occur two or three days after the four daily doses have been given.

Contraindications

1. *Pre-existing Genital or Breast Carcinoma, with Some Exceptions.* The possibility of exogenous estrogens acting as inciting agents in some cases of carcinoma of the breast or genital tract is a subject of controversy among authorities. Since ENOVID exerts estrogenic activity, the presence of carcinoma in either of these areas should be ruled out before therapy is instituted.

2. *Pre-existing Liver Disease, Dysfunction or Jaundice.* In suspected or overt liver dysfunction or disease ENOVID should not be used. The status of liver function in ENOVID-treated patients must be followed closely.

3. *Previous Thrombophlebitis or Pulmonary Embolism.* ENOVID and ENOVID-E are contraindicated in these patients unless the reason for its use in the judgment of the physician is overwhelming.

Precautions

For prevention of conception the drug is only recommended for periods of use up to four years. Longer-term use has not yet been established as safe.

At the discretion of the attending physician, during this period the drug should be used primarily when pregnancy is contraindicated or should be avoided.

Multiple detectable functional changes in the endocrine system with particular reference to the thyroid, adrenal and pituitary glands and perhaps the ovary occur in ENOVID-treated patients. The long-term effect on the pituitary, adrenal and thyroid glands and on liver metabolism is not yet clearly established although observations made on long-term users of ENOVID reveal some changes (discussed later). The present experience indicates that endocrine function typical for the individual patient prior to treatment with ENOVID returns promptly when medication is stopped.

The first intermenstrual interval after discontinuing ENOVID therapy is usually prolonged; thus a patient for whom a twenty-eight-day cycle is usual might not menstruate for thirty-five days or longer. Ovulation in such prolonged cycles will occur correspondingly later in the cycle. Succeeding cycles, however, are usually typical for the individual patient prior to therapy with ENOVID. Occasionally amenorrhea or menstrual irregularities persist for months.

A biopsy taken late in the cycle when ENOVID is given from the fifth through the twenty-fourth day of the cycle will reveal a definitely edematous stroma containing pseudodecidual cells similar in appearance to the decidual cells seen in the endometrium of early pregnancy, increased vascular development and relatively sparse glands with scanty secretion. Because of this pseudodecidual activity, mention of ENOVID therapy should accompany biopsy specimens when sent to the pathology laboratory for examination.

The question of androgenic effects of a progestin is of importance whenever the drug is prescribed for long-term use. One case of fetal masculinization has been reported in connection with ENOVID administration, but the author later stated that the incident was probably coincidental. Clinically, ENOVID has manifested no evidence of androgenicity and, in fact, is estrogenic and progestational in its actions. Nevertheless, the physician should take these reports into account when prescribing the drug.

Early reports that cervical erosion was worsened by ENOVID therapy have not been substantiated by subsequent investigation. However, patients receiving ENOVID should receive periodic vaginal examinations and any cervical erosion found should be treated by accepted means.

Patients on ENOVID therapy may show an increase in protein bound iodine and butanol extractable iodine and a decrease in T^3 values. These results do not necessarily correlate with any change in the clinical state of these patients regarding thyroid function and may reflect an increase in thyroxine binding protein similar to the increase known to follow administration of estrogens. Thyroid enlargement may occur rarely.

There is no direct evidence that ENOVID alters the diabetic state. However, in a few instances some degree of difficulty in the management of diabetic patients has been reported in connection with ENOVID therapy. It is possible that a change in insulin dosage may be required. For this reason diabetic patients should be closely observed while ENOVID is being administered. They may be expected to return to their pretreatment manageability on discontinuance of the drug.

Patients with rheumatoid arthritis receiving very high doses of ENOVID over a long period of time have been reported to show an increased bromsulphalein retention. Inconsistent and irregular moderate bromsulphalein retention has also been reported in patients receiving lower doses of ENOVID cyclically. However, preliminary investigations indicate that this has not been a significant problem. Nevertheless, cholestatic jaundice has been reported in a few instances in patients receiving ENOVID, and ENOVID will apparently induce the rare syndrome of familial jaundice of pregnancy. For this reason the administration of ENOVID to women with liver or biliary tract disease or dysfunction or a history of such disease or jaundice is contraindicated, unless the reason for such use in the opinion of the physician is overwhelming.

The status of liver function in ENOVID-treated patients must be followed closely.

It has now been accepted that one of the gonadotropin hormones of the anterior pituitary gland (the luteotropic hormone, L.T.H.) is identical to the lactogenic hormone. Since a principal action of ENOVID is the suppression of gonadotropic hormones, it is likely that ENOVID will suppress lactation if administered to a nursing mother. Suppression of lactation is less likely, however, if medication is delayed six to eight weeks post partum, when lactation is well established.

An occasional patient receiving ENOVID may experience psychic depression, although the relationship of ENOVID administration to such a response is by no means clear.

Epileptiform convulsions have been reported to occur in women receiving ENOVID. Since ENOVID may cause salt and water retention an exacerbation of

the epileptic state might be expected from this cause. Conversely, some epileptic patients whose attacks primarily occur premenstrually have been relieved of their attacks.

There is no evidence that ENOVID is etiologic in the production of uterine fibroids, although pre-existing fibroids frequently increase in size while ENOVID is being given. Discontinuance of therapy ordinarily results in a regression.

That several hundred instances of peripheral thrombophlebitis and embolism, including fatalities due to embolic phenomena, have occurred in women receiving ENOVID has received considerable attention. The possible causal relationship of ENOVID administration to these incidents has received considerable study and has been reviewed by four committees of recognized authorities.

Any relationship between a state of "hypercoagulability" and thromboembolic disease still remains undetermined. In any event, presently available data do not establish—or exclude—the possibility that ENOVID produces hypercoagulability as defined by increases in components or acceleration of clotting kinetics. A number of blood coagulation factors are known to be modified during normal pregnancy. These include fibrinogen, fibrinolysin, prothrombin, factors VII, VIII and X, and other complicated measurements of the blood coagulation mechanism. ENOVID also produces changes in these factors in the same directions as those observed during pregnancy. Although the significance of these changes is presently unknown, additional studies are in progress.

ENOVID was first distributed commercially in June 1957. As of June 1963, somewhat more than 400 thromboembolic episodes have been reported among ENOVID users with thirty-seven fatalities in the United States as a result of the development of pulmonary embolism. On further investigation some of these cases and fatalities were unrelated to thromboembolic disease or the histories revealed definitive and generally-recognized causes for the development of the reported condition. Among the fatalities, more than one-third could be classified as idiopathic or having no clear cut (precipitating) etiologic factor.

Available medical and statistical evidence relative to the incidence of thromboembolic episodes in non-medicated and nonpregnant women of childbearing age is singularly sparse and not completely reliable. Studies are in progress to attempt to rectify this defect in knowledge of the incidence of thrombophlebitis and pulmonary embolism in this segment of the female population. The *expected* incidence of thromboembolic episodes in "healthy" young women is difficult to determine from the available data but there is evidence that in such women in the age range of 20 to 44 years, not subjected to trauma and not pregnant, 926 cases of thrombophlebitis per million per year will occur, that among these sixty cases of pulmonary embolism will be seen and that 7.9 will die as a result of thrombophlebitis or pulmonary embolism.

A recent panel survey (February-August 1963, J.A.M.A. *185:*776 [Sept. 7] 1963) in analyzing the 1962 fatalities by age groups did not find a statistically significant increased rate of fatalities in any age group. Since the possibility of a real increase especially in the older age group remains this should be carefully weighed by the physician prescribing ENOVID. Further data will be evaluated and reported.

There is abundant evidence in the literature to support the concept that the incidence of thrombotic episodes increases with age, with parity, with obesity, with a history of previous occurrences, with a history of varicose veins or other vascular abnormality, with trauma or unusual activity, and with restricted movement combined with an interference with the dependent circulation (long automobile or airplane trips). Similar causal or contributory factors have been noted in the histories of many of the cases reported as occurring during ENOVID administration. Women subject to such exposure or exhibiting these characteristics should be considered as being at risk of thrombosis.

Side Actions

The most frequently encountered side action to ENOVID therapy is nausea, less commonly vomiting.

It is also apparent that side actions are more prevalent in the first cycle of treatment and that they fall sharply on continuation of therapy. After the third cycle the incidence is low.

Nausea may be controlled by instructing the patient to take the tablet with meals or with a glass of milk at bedtime or by recommending that an antacid or an antinauseant preparation be taken with the tablet of ENOVID.

Spotting or breakthrough bleeding may occur; usually this is evidence of inadequate dosage. This type of bleeding is usually controlled by increasing the daily dosage of ENOVID. The first increment of such additional dosage should be taken as soon as spotting is noticed. This increased dosage may be required for only four or five days after which the original schedule may be resumed.

The menstrual flow associated with ENOVID therapy is usually typical of the individual patient although it may be scanty or, less commonly, more profuse. In uncommon instances an endometrial cast may be produced.

Vaginal bleeding occasionally occurs after several months of the cyclic use of ENOVID therapy. When this is observed careful search for the presence of an organic lesion is indicated. Patients on long-term ENOVID medication should have annual or more frequent pelvic examinations.

Amenorrhea is a phenomenon encountered occasionally in instances when ENOVID is prescribed cyclically. The term is used to describe an absence of menstrual flow during the periodic omission of ENOVID to permit the patient to menstruate. In spite of the fact that no menstrual flow occurs in the missed or amenorrheic period, this phenomenon does not preclude ovulation during the following cycle. Sometimes ovulation may occur as early as nine or ten days after medication is so stopped. Thus, it is most important to instruct the patient to begin to take the ENOVID tablets for another twenty days and to begin taking them again no later than one week after the last tablet was taken.

Sodium retention with edema is encountered and usually may be treated satisfactorily by salt restriction or controlled by judicious selection and use of a diuretic agent. For this reason, however, ENOVID should be used with caution in patients with cardiac or renal disorders or hypertension.

As previously stated ENOVID may be used for the treatment of premenstrual tension and may prove successful. However, an aggravation of premenstrual tension occurs occasionally, presumably as a result of the sodium retention to which reference has been made.

The occurrence of chloasma has been reported. The degree of pigmentation varies widely and persists, usually at a stationary level, throughout the course of medication. On discontinuing medication the pigmentation usually disappears but, as in the postpartum patient, it may persist for varying lengths of time.

An occasional patient may experience photosensitivity dermatitis or urticaria. Miscellaneous cutaneous conditions occurring during administration

of ENOVID have also been reported (erythema multiforme and nodosum, hemorrhagic eruption, lupus erythematosus and acne).

Breast changes similar to those encountered in early pregnancy may be manifested. Patients receiving ENOVID for appreciable periods of time may occasionally exhibit weight gain. It is not determined whether this represents an anabolic effect or is merely the result of a psychologic effect such as freedom from the fear of pregnancy.

Loss of scalp hair or excessive growth of body hair has been reported occasionally. It is not yet clear as to the exact relationship of ENOVID administration to this manifestation (which is seen only rarely) but from studies now in progress it appears that such changes when they occur are more closely identified with similar changes in hair growth pattern seen during pregnancy and in the postpartum period than with other possible mechanisms.

Headache, dizziness, diarrhea and abdominal pain have been reported occasionally.

How Supplied

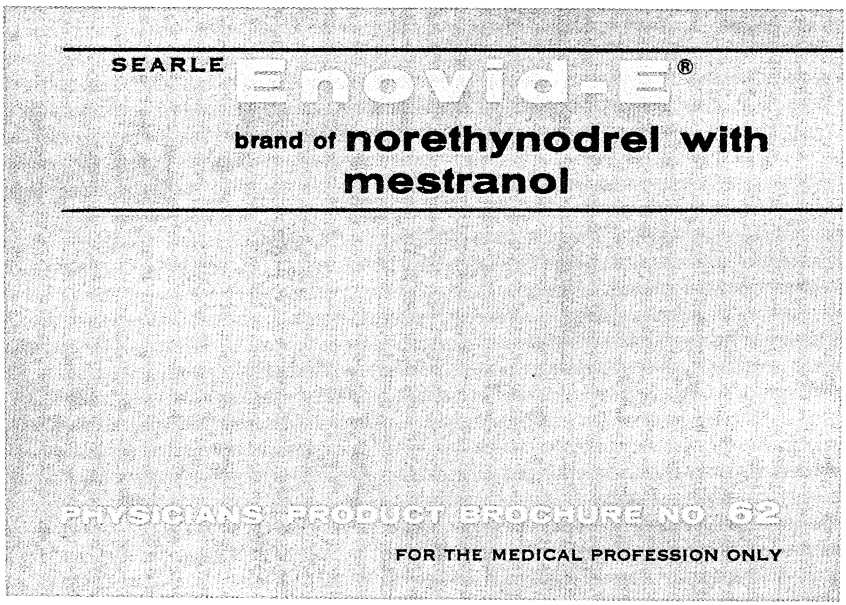
ENOVID-E

2.5-mg. (debossed E on one side and debossed SEARLE on the other side), uncoated, unscored, pale pink tablets containing 2.5 mg. of norethynodrel and 0.1 mg. mestranol; boxes of 120 and 600 (6 and 30 Calendar-Packs™ of 20 tablets each), and bottles of 250.

ENOVID

5-mg. (debossed 5 on one side and debossed SEARLE on the other side), unscored, uncoated, light pink tablets containing 5 mg. of norethynodrel and 0.075 mg. of mestranol; boxes of 120 and 600 (6 and 30 Calendar-Packs™ of 20 tablets each), and bottles of 100 and 500.

10-mg. (debossed 10 on one side and debossed SEARLE on the other side), unscored, uncoated, coral-colored tablets containing 9.85 mg. of norethynodrel and 0.15 mg. of mestranol; bottles of 50 and 500.


SEARLE
Enovid-E®
brand of norethynodrel with mestranol
PHYSICIANS' PRODUCT BROCHURE NO. 62
FOR THE MEDICAL PROFESSION ONLY

For Contraception

PREPARED BY THE MEDICAL DEPARTMENT OF G. D. SEARLE & CO.
CHICAGO, ILLINOIS 60680

Table of Contents

ethnic groups in clinic and private practice to confirm the efficacy, safety and acceptability of this dosage form. At the end of the third quarter of 1963, 2,946 women had participated in Enovid-E trials for from one to forty-six cycles for a total of 33,416 cycles, as indicated in Tables I and II.

In no instance did pregnancy occur during cyclic administration[1, 2, 4, 6, 15-24] *of Enovid-E when taken as directed. A substantial number of these women were well into their third year of continuous cyclic medication with Enovid-E by the third quarter of 1963.*

No serious manifestations of toxicity have been observed in any of these women, and normal or pretreatment physiologic

TABLE I. NUMBER OF WOMEN IN CLINICAL STUDIES TAKING ENOVID-E ACCORDING TO CYCLES OF USE

Clinical Groups	1st-5th	6th-11th	12th-17th	18th-23rd	24th-29th	30th-36th	Over
Wiseman[5] (Slough, England)	782	364	241	134	56	12	7
Binks[6] (Australia)	64	47	23	18	13	11	9
Wisdom[7] (London)	235	209	182	123	47	2	—
Chinnatamby[8] (Ceylon)	673	139	48	—	—	—	—
Satterthwaite[9] (Humacao, P.R.)	94	75	55	41	30	12	10
Comparative Study[10]	198	164	112	78	31	—	—
Tyler[11] (Los Angeles)	106	101	83	73	35	4	3
García and Pincus[12]* (San Juan, P.R.)	413	291	204	168	102	56	48
Flowers[13] (Chapel Hill, N.C.)	245	214	130	76	37	1	—
Burket[14] (Cincinnati, Ohio)	136	113	95	37	11	—	—
	2,946	1,717	1,173	748	362	98	77

The above tabulation shows that at least 362 women were in the third year or more of medication with Enovid-E.

*In this study 234 women received other dosage forms of Enovid before taking Enovid-E for from one to fifty-six cycles and 118 of this group were in their fourth year or more of medication with Enovid and Enovid-E at the end of April 1963.

TABLE II. SUMMARY OF CLINICAL EXPERIENCE WITH ENOVID-E

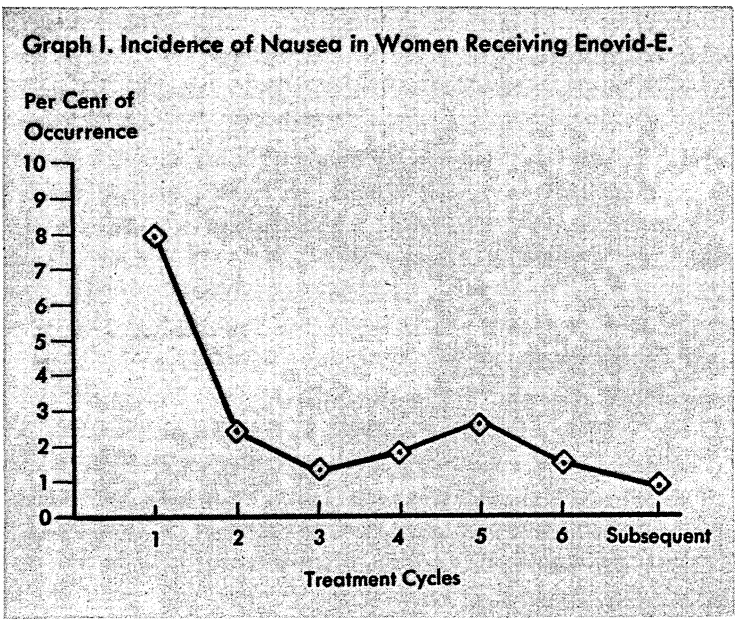
Clinical Group	Total Cycles of Use
Wiseman[5]	6,299
Binks[6]	843
Wisdom[7]	3,967
Chinnatamby[8]	3,453
Satterthwaite	
Humacao[9]	1,525
Comparative[10]	2,443
Tyler[11]	2,092
Pincus[12]*	6,138
Flowers[13]	2,975
Burket[14]	1,841
Mears[4]	181
Andrews and Andrews[17]	521
Mears[19]	1,228
	33,416
*Other dosage forms of Enovid	5,321
	38,737

function is resumed promptly when medication is discontinued for any reason. *This is illustrated by Satterthwaite's observations*[24] *of ninety-six women, most of whom received a larger dose of medication than that contained in Enovid-E, and who discontinued taking tablets after twelve or more months.* Within one month after discontinuing medication 44.8 per cent (forty-three) were pregnant and 82.3 per cent (seventy-nine) were pregnant within the next four months. All but four of the remaining seventeen were known to be using other methods of contraception or were separated from their consorts.

The fact that normal women ovulate and menstruate regularly after discontinuing medication with Enovid or Enovid-E indicates that there is no *discernible* untoward effect on post-treatment gonadotropin activity of the anterior pituitary gland. Neither is there any evidence of an adverse effect on the elaboration of other anterior pituitary hormones.

The ovum-producing capacity after cyclic administration of larger doses than those contained in Enovid-E has been investigated[2] by García, Rock and Pincus. A determination was made

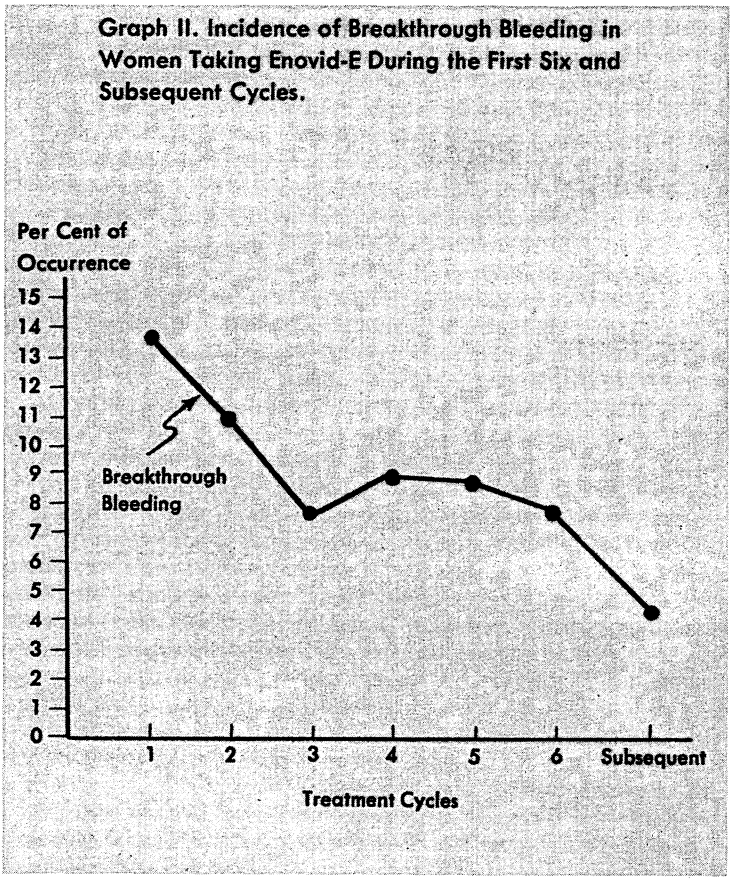
by actual count of the number of primordial follicles in the ovaries of women receiving Enovid and of untreated women. The follicle counts in the ovaries from Enovid-treated women included those from women who had received Enovid cyclically (menstrual cycle day 5 through day 24) for as long as twenty cycles. In no instance was there any significant variation from the normal count of ovarian primordial follicles.



DOSAGE AND ADMINISTRATION

ONE tablet of Enovid-E should be prescribed daily for twenty (20) consecutive days for each menstrual cycle, beginning five (5) days after the onset of menstruation. Menstruation will usually occur one to three days after the last tablet is taken.

Early ovulation is a possibility during the *first* treated cycle. Advising the patient to use an additional means of protection



for the *first* week of the *first* Enovid-E-treated cycle may be desirable.

CONTRAINDICATIONS

1. Pre-existing Genital or Breast Carcinoma, with Some Exceptions. The possibility of exogenous estrogens acting as inciting agents in some cases of carcinoma of the breast or genital tract is a subject of controversy among authorities.

Since Enovid-E exerts estrogenic activity, the presence of carcinoma in either of these areas should be ruled out before therapy is instituted.

2. *Pre-existing Liver Disease, Dysfunction or Jaundice.* In suspected or overt liver dysfunction or disease Enovid-E should not be used. The status of liver function in these patients treated with Enovid-E must be followed closely.

3. *Previous Thrombophlebitis or Pulmonary Embolism.* Enovid-E is contraindicated in these patients unless the reason for its use in the judgment of the physician is overwhelming.

PRECAUTIONS

THE maximal patient exposure to Enovid-E, as of May 1963, was forty-six cycles and a significant number of women were well into their third year of continuous cyclic medication. In one study[12], however, 234 women received other dosage forms of Enovid before taking Enovid-E and more than one-half of these women were in their fourth year or more of Enovid medication at the end of April 1963. Nevertheless, since the bulk of clinical experience with Enovid-E does not extend beyond three years and owing to any unanticipated effect on the ovaries, uterus, pituitary and adrenal glands or other body organs, duration of use longer than thirty-nine cycles (three years) must await the results of continuing studies.

Multiple detectable functional changes in the endocrine system with particular reference to the thyroid, adrenal and pituitary glands and perhaps the ovary occur in women treated with Enovid-E. The long-term effect on the pituitary, adrenal and thyroid glands and on liver metabolism is not yet clearly established although observations made of long-term users of Enovid-E reveal some changes (discussed later). The present experience indicates that endocrine function typical for the individual woman prior to treatment with Enovid-E usually returns promptly when medication is stopped.

Prolongation of First Post-Treatment Intermenstrual Interval. The first intermenstrual interval after discontinuing Enovid-E

therapy is usually prolonged; thus a woman for whom a twenty-eight-day cycle is usual might not menstruate for thirty-five days or longer. Ovulation in such prolonged cycles may occur correspondingly later in the cycle. Succeeding cycles, however, are usually typical for the individual woman prior to therapy with Enovid-E. Occasionally amenorrhea or menstrual irregularities persist.

Endometrial Effects. The characteristic action of Enovid-E on the endometrium is of considerable importance when biopsies are taken during or after therapy. As discussed in the section on *Human Pharmacology*, a biopsy taken late in the cycle when Enovid-E is given from the fifth through the twenty-fourth day of the cycle will reveal a definitely edematous stroma containing pseudodecidual cells (similar in appearance to the decidual cells in the endometrium of early pregnancy), increased vascular development and relatively sparse glands with scanty secretion. Because of this pseudodecidual activity, mention of Enovid-E therapy should accompany biopsy specimens when sent to the pathology laboratory for examination.

Androgenic Effects. The question of androgenic effects of a progestin is of importance whenever the drug is prescribed for long-term use. One case of fetal masculinization has been reported[25] in connection with Enovid administration, but the author[26] later stated that the incident was probably coincidental. Clinically, Enovid-E has manifested no evidence of androgenicity and, in fact, is estrogenic and progestational in its actions. Nevertheless, the physician should take this report into account when prescribing the drug.

Cervical Erosion. Early reports that cervical erosion was worsened by Enovid therapy have not been substantiated[27] by subsequent investigation. However, women receiving Enovid-E should receive periodic vaginal examinations and any cervical erosion found should be treated by accepted means.

Thyroid Function. Women on Enovid-E therapy may show an increase in protein bound iodine[21, 28] and butanol extractable iodine and a decrease in T^3 values. These results do not

necessarily correlate with any change in the clinical state of these women regarding thyroid function and may reflect an increase in thyroxine binding protein similar to the increase known to occur after the administration of estrogens. Thyroid enlargement rarely occurs.

Diabetes. There is no direct evidence that Enovid alters the diabetic state. However, in a few instances some degree of difficulty in the management of diabetic patients has been reported in connection with Enovid therapy. It is possible that a change in insulin dosage may be required. For this reason diabetic patients should be closely observed while Enovid-E is being administered. They may be expected to return to their pretreatment manageability on discontinuance of the drug.

Liver Function. Patients with rheumatoid arthritis receiving very high doses of Enovid over a long period of time have been reported[29] to show an increased bromsulphalein retention. Inconsistent and irregular moderate bromsulphalein retention has also been reported[30] in women receiving lower doses of Enovid cyclically. However, preliminary investigations indicate[28] that this has not been a significant problem. Nevertheless, cholestatic jaundice has been reported in a few instances of women receiving Enovid, and Enovid will apparently induce the rare syndrome of familial jaundice of pregnancy. For this reason the administration of Enovid-E to women with liver or biliary tract disease or dysfunction or a history of such disease or of jaundice is contraindicated, unless the reason for such use in the opinion of the physician is overwhelming.

The status of the liver function of these women treated with Enovid-E must be followed closely.

Lactation. It has now been accepted that one of the gonadotropin hormones of the anterior pituitary gland (the luteotropic hormone, L.T.H.) is identical to the lactogenic hormone. Since a principal action of Enovid is the suppression of the gonadotropic hormones, it is likely that Enovid-E will suppress lactation if administered to a nursing mother. Suppression of

lactation is less likely, however, if medication is delayed[21] six to eight weeks post partum, when lactation is well established.

Central Nervous System. An occasional woman receiving Enovid may experience psychic depression, although the relationship of Enovid administration to such a response is by no means clear.

Epileptiform convulsions have been reported to occur in women receiving Enovid. Since Enovid may cause salt and water retention an exacerbation of the epileptic state might be expected from this cause. Conversely, some epileptic patients whose attacks primarily occur[31, 32] premenstrually have been relieved of their attacks.

Fibroids. There is no evidence that Enovid is etiologic in the production of uterine fibroids, although pre-existing fibroids frequently increase in size while Enovid is being given. Discontinuance of therapy ordinarily results in a regression.

Thrombophlebitis. Considerable attention has been given to the several hundred instances of peripheral thrombophlebitis and embolism (including fatalities due to embolic phenomena) occurring in women receiving Enovid. The possible causal relationship of Enovid administration to these incidents has received much study and has been reviewed by four committees of recognized authorities.

Any relationship between a state of "hypercoagulability" and thromboembolic disease still remains undetermined. In any event, presently available data do not establish – or exclude – the possibility that Enovid produces hypercoagulability as defined by increases in clotting components or acceleration of clotting kinetics. A number of blood coagulation factors are known to be modified during normal pregnancy. These include fibrinogen, fibrinolysin, prothrombin, factors VII, VIII and X, and other complicated measurements of the blood coagulation mechanism. Enovid also produces[33-51] changes in these factors in the same directions as those observed during pregnancy. Although the significance of these changes is presently unknown, additional studies are in progress.

Enovid was first distributed commercially in June 1957. As

HOW SUPPLIED

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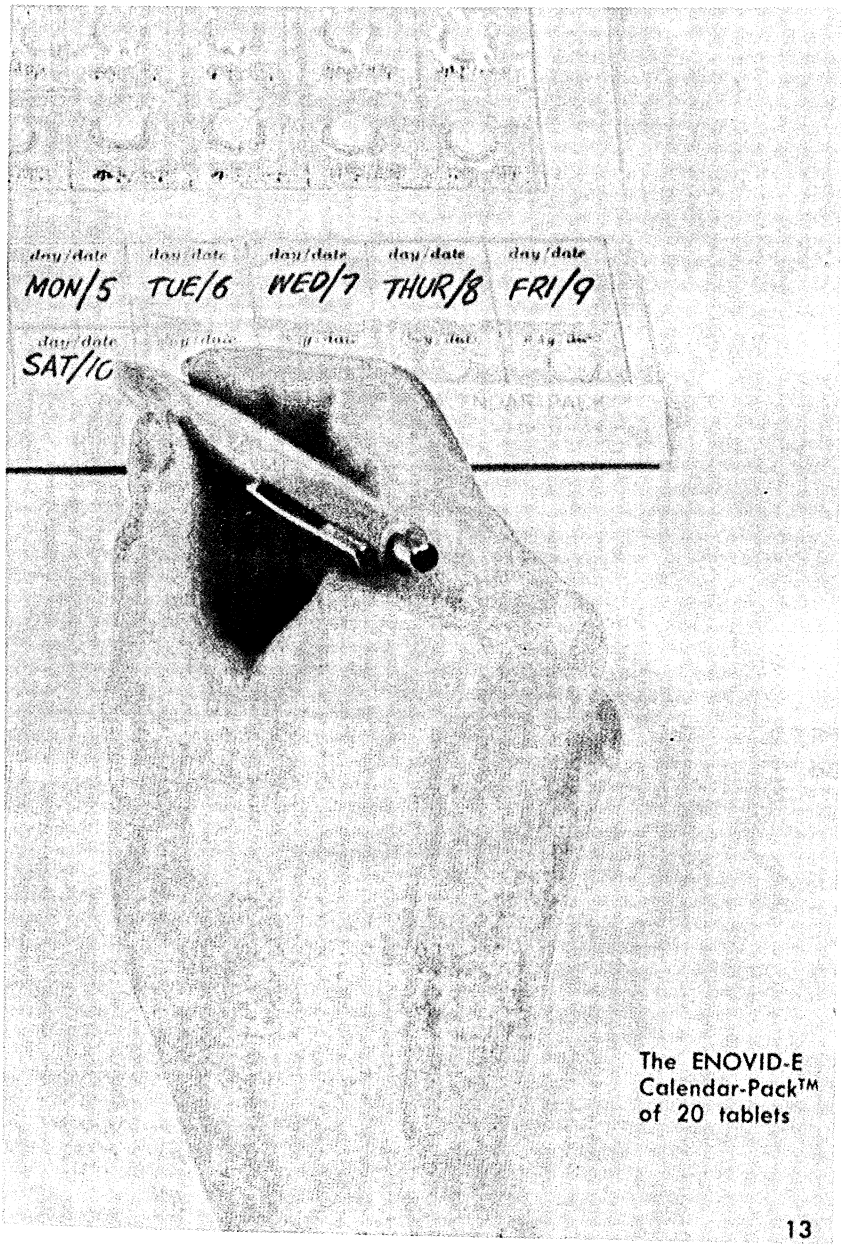
12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WED/7
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THUR/8
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FRI/9
day/date
SAT/10
The ENOVID-E
Calendar-Pack™
of 20 tablets
13

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A recent panel survey[52] (February-August 1963) in analyzing the 1962 fatalities by age groups did not find a statistically significant increased rate of fatalities in any age group. Since the possibility of a real increase, especially in the older age group, remains this should be carefully weighed by the physician prescribing Enovid. Further data will be evaluated and reported.

There is abundant evidence in the literature to support the concept that the incidence of thrombotic episodes increases[53, 54] with age, parity, obesity, a history of previous occurrences, a history of varicose veins or other vascular abnormality, with trauma or unusual activity, and restricted movement combined with interference[55] with the dependent circulation (long automobile or airplane trips). Similar causal or contributory factors have been noted in the histories of many of the cases reported as occurring during Enovid administration. Women subject to such exposures or exhibiting these characteristics should be considered as being at risk of thrombosis.

It seems a reasonable conclusion that these women should be closely observed for the development of thromboembolic

disease, whether or not they are receiving Enovid, particularly when they present signs and symptoms suggestive of acute pulmonary disease, even in the absence of clinical signs of peripheral thrombosis.

SIDE ACTIONS

SIDE actions are more prevalent in the first cycle of treatment but fall sharply on continuation of therapy. After the third cycle the incidence is low. See Graphs I and II (pages 6-7) and Table III.

TABLE III. OCCURRENCE OF SIDE EFFECTS IN EARLY CYCLES[9-13]

Cycle	% of Patients with Nausea	% of Patients with Breakthrough Bleeding	Number of Cycles
1	8.1	13.6	1,053
2	2.3	10.9	1,020
3	1.3	7.5	974
4	1.8	9.0	703
5	2.7	8.9	660
6	1.4	7.9	629
Subsequent	0.9	4.3	10,311
All cycles	1.7	6.2	15,290
(Total Patients — 1,053)			

N.B. — "Spotting" is not included in breakthrough bleeding.

Nausea may be controlled by instructing the patient to take the tablet with meals or with a glass of milk at bedtime or by recommending that an antacid or an antinauseant preparation be taken with the tablet of Enovid-E.

Spotting, Breakthrough Bleeding. Spotting or breakthrough bleeding may occur; usually this is evidence of inadequate dosage. This type of bleeding is usually controlled by increasing the daily dose of Enovid-E. The first increment of such an increased dose should be taken as soon as spotting is noticed. This increased dose may be required for only four or five days after which the original schedule may be resumed.

If any irregular bleeding occurs a careful search for an organic lesion is indicated. Women on long-term medication should have at least annual or more frequent pelvic examinations.

Alterations in Menstrual Flow. The menstrual flow associated with Enovid-E therapy is usually typical of the individual woman although it may be scanty or, less commonly, more profuse. In uncommon instances possibly an endometrial cast may be produced.

Amenorrhea (Missed Menstruation). This is a phenomenon encountered occasionally in women when Enovid-E is prescribed cyclically. The term is used to describe an absence of menstrual flow during the periodic omission of Enovid-E to permit the woman to menstruate. In spite of the fact that no menstrual flow occurs in the missed or amenorrheic period, this phenomenon does not preclude ovulation during the following cycle. Sometimes ovulation may occur as early as nine or ten days after medication is so stopped. *Thus, it is most important to instruct the woman to take the Enovid-E tablets for another twenty days and to begin taking them again no later than one week after the last tablet in the previous cycle was taken.*

Edema. Sodium retention with edema may be encountered and usually is satisfactorily treated by salt restriction or controlled by the judicious use of a diuretic agent. For this reason, however, Enovid-E should be used with caution in patients with cardiac or renal disorders or hypertension.

Skin Changes (manifestations). The occurrence of chloasma has been reported by Satterthwaite[24] and others[28]. The degree of pigmentation varies widely and persists, usually at a stationary level, throughout the course of medication. On discontinuing medication the pigmentation usually disappears but, as in the postpartum patient, it may persist for varying lengths of time. An occasional woman may experience photosensitivity dermatitis or urticaria. Miscellaneous cutaneous conditions occurring during administration of Enovid have also been reported (erythema multiforme and nodosum, hemorrhagic eruption, lupus erythematosus and acne).

Miscellaneous. Breast changes similar to those encountered in early pregnancy may be manifested. Women receiving Enovid for appreciable periods of time may occasionally exhibit weight gain or loss. It has not been determined whether the gain in weight represents an anabolic effect or is merely the result of a psychologic effect such as freedom from the fear of pregnancy.

Loss of scalp hair or excessive growth of body hair has been reported occasionally. It is not yet clear as to the exact relationship of Enovid administration to this manifestation (which is only rarely seen) but from studies now in progress it appears that such changes, when they occur, are more closely identified with similar changes in the hair-growth pattern seen during pregnancy and in the postpartum period than with other possible mechanisms.

Headache, dizziness, diarrhea and abdominal pain have been reported occasionally.

TABLE IV. WEIGHT CHANGE[1] OF PATIENTS ON ENOVID-E

Weight Change	Number of Patients	Per Cent
None	1	1.0
Gain 1 - 5 lbs.	19	18.1
6 - 10	20	19.0
11 - 15	8	7.6
16+	3	2.9
Total gaining	50	47.6
Loss 1 - 5 lbs.	18	17.1
6 - 10	26	24.8
11 - 15	4	3.8
16+	6	5.7
Total losing	54	51.4
Total patients	105	100.0

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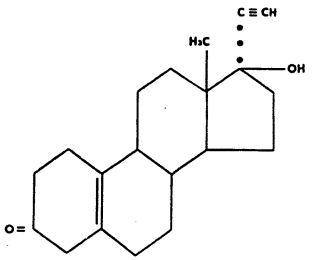
CHEMISTRY

ENOVID, brand of norethynodrel with mestranol, is composed principally of 17*a*-ethynyl-17-hydroxy-5(10)-estren-3-one; it may be represented structurally as follows:



Enovid-E tablets contain 2.5 mg. of norethynodrel and 0.1 mg. of mestranol.

HUMAN PHARMACOLOGY

ACTION ON THE ENDOMETRIUM. When Enovid is given from the fifth through the twenty-fourth day of the cycle to normal or to anovulatory women or to those with an inadequate secretory phase (providing adequate estrogen is secreted) a different endometrial picture will be found. Biopsy specimens of such endometria, taken on the twentieth to the twenty-second day of the cycle, will reveal a definite stromal and vascular development with sparse glands which show varying stages of secretory exhaustion. This has been well described[56] by Rock, García and Pincus. Such an endometrium is similar to that present in early pregnancy and may be termed a pseudodecidual type.

From a study of biopsy specimens taken between the fifth and twenty-fifth day after the administration of Enovid, Pincus[57] has found that the progress of endometrial development just described does occur. Those taken from normal women between the fourth and tenth days of medication reveal a typical succession of secretory phase development. A definite development of stromal tissue and increased vascularity with a relative decrease in the number of glands occur

as biopsy specimens are taken progressively later during the therapeutic course. Finally, late in the course, the predecidual reaction already referred to occurs and this type of endometrium is usually maintained without breakdown or bleeding for a prolonged period if proper Enovid-E administration is continued.

ACTION ON GONADOTROPIN EXCRETION. It has been clearly demonstrated in animals that Enovid administration reduces the gonadotropin content of and secretion by the anterior pituitary gland; a similar action has been demonstrated[58] in man. Pincus[57], and Kupperman and Epstein[59] report a sharp reduction in gonadotropin excretion by women during Enovid administration. Suppression of gonadotropins readily explains the observed effects of the drug.

Additional details of clinical and laboratory observations are included in Searle Physicians' Product Brochure No. 67.

Essential Information for Physicians on the Clinical Application of Enovid-E

1. PRESCRIBE one tablet daily beginning on day 5 of the cycle and continuing through day 24. Begin medication on day 5 *whether or not* menstrual flow has ceased.

2. Admonish regarding regularity of taking medication as directed. Regularity applies not only to the days of the cycle but also to the time of day that the tablet is taken. A tablet taken in the morning of one day and another in the evening of the next day may result in an interval of thirty-six hours between doses. If a tablet is forgotten, it should be taken when remembered, but the regular tablet for that day also should be taken at the regular time.

3. Instruct the woman to increase the dose for five days if spotting or breakthrough bleeding occurs. If the spotting is very slight, she may ignore it with the expectancy that it will not occur in later cycles.

4. Provide for an adequate supply of tablets in the event the daily dose must be increased.

5. If two episodes of spotting occur in the first treated cycle, women may require a larger daily dose.

6. If one episode of spotting occurs during each of the first four treated cycles, women may require a larger daily dose. If irregular bleeding occurs the possibility of an organic lesion should be explored.

7. Instruct the woman to resume medication seven days after completion of previous course in the event that anticipated menstruation fails to appear. The possibility of pregnancy should be investigated in the event that the tablets were not taken as directed.

8. Advise regarding the increased possibility of conception if instructions are not followed.

9. Advise additional means of control during the first seven days that Enovid-E is taken in the *first treated cycle* because of the possibility of early ovulation.

10. Interrogate regarding occurrence of nausea during previous pregnancy. If it has occurred employ device to avoid Enovid-induced nausea by prescribing an antiemetic as suggested on page 15.

11. If nulliparous, determine desirability of discussion regarding possibility of nausea and prescribing an antiemetic.

12. Final admonition regarding importance of taking medication regularly and specifically as directed.

13. Instructions for women in the use of Enovid have been prepared for distribution to them by the physician if desired. These instructions may be obtained from G. D. Searle & Co., or from company representatives. In addition, a booklet discussing Enovid in some detail and written in lay language is similarly available.

REFERENCES

1. Rice-Wray, E.: Proceedings of a Symposium on 19-Nor Progestational Steroids: Field Study with Enovid as a Contraceptive Agent, Chicago, Searle Research Laboratories, 1957, pp. 78-85.
2. García, C.-R.; Rock, J., and Pincus, G.: Proceedings of a Symposium on Enovid: Observations on Prolonged Administration of Enovid, Chicago, Searle Research Laboratories, 1959, pp. 35-41.
3. Eckstein, P., and others: The Birmingham Oral Contraceptive Trial, Brit. Med. J. 2:1172-1179 (Nov. 4) 1961.
4. Mears, E.: Clinical Trials of Oral Contraceptives, Brit. Med. J. 2:1179-1183 (Nov. 4) 1961.
5. Wiseman, A.: Investigator's Clinical Report, April 15, 1963; this is a continuation of the published report, Reference #18.
6. Binks, R.; Cambourn, P., and Papworth, R. A.: Preliminary Report of a Clinical Trial of Oral Norethynodrel for Fertility Control, Med. J. Australia 1:716-717 (May 12) 1962.
7. Wisdom, C.: Investigator's Clinical Report, Dec. 23, 1963.
8. Chinnatamby, S.: Clinical Trial of Oral Contraceptives, Annual Report, Family Planning Association of Ceylon, Colombo, 1963, pp. 23-26.
9. Satterthwaite, A. P.: Investigator's Clinical Report, April 30, 1963.
10. Satterthwaite, A. P.: Investigator's Clinical Report, May 10, 1963.
11. Tyler, E. T.: Investigator's Clinical Report, March 31, 1963.
12. García, C.-R., and Pincus, G.: Investigators' Clinical Report, April 30, 1963.
13. Flowers, C. E.: Investigator's Clinical Report, June 27, 1963.
14. Burket, R.: Investigator's Clinical Report, July 30, 1963.
15. Pincus, G., Suppression of Ovulation with Reference to Oral Contraceptives, in Gardiner-Hill, H. (editor): Modern Trends in Endocrinology, 2nd series, London, Butterworth & Co. (Publishers), Ltd., 1961, pp. 231-245.
16. Jackson, M. H.: Observations on the Use of Certain Orally Active Progestogens for the Control of Fertility in Women, Proc. Roy. Soc. Med. 54:16-19 (Nov.) 1961.
17. Andrews, W. C., and Andrews, M. C.: Use of Progestins for Oral Contraception, Southern Med. J. 55:454-456 (May) 1962.
18. Pullen, D.: 'Conovid-E' as an Oral Contraceptive, Brit. Med. J. 2:1016-1019 (Oct. 20) 1962.
19. Mears, E.: A Comparative Study of Three Available Oral Contraceptives, J. Reprod. Fertil. 4:229-230 (Oct.) 1962.
20. Pincus, G.: Control of Reproduction in Mammals, in Wolstenholme, G. (editor): Man and His Future, Boston, Little, Brown & Co., 1963, pp. 79-90.
21. García, C.-R., and Pincus, G.: Ovulation Inhibition by Progestin-Estrogen Combination, presented at the International Fertility Association Meeting in Brussels, Belgium, March 2-3, 1963, in press.
22. Jackson, M. C. N.: Oral Contraception in Practice (The Sixth Oliver Bird Lecture), J. Reprod. Fertil. 6:153-173 (Aug.) 1963.
23. Satterthwaite, A. P., and Gamble, C. J.: Conception Control with Norethynodrel: Progress Report of a Four-Year Field Study at Humacao, Puerto Rico, J. Amer. Med. Women's Ass. 17:797-802 (Oct.) 1962.
24. Satterthwaite, A. P.: Control of Ovulation with Norethynodrel; Progress Report of a Five-Year Field Study at Humacao, Puerto Rico, presented at the Fourth World Congress on Fertility in Rio de Janeiro, Aug. 8-15, 1962, in press.
25. Grumbach, M. M.; Ducharme, J. R., and Moloshok, R. E.: On the Fetal Masculinizing Action of Certain Oral Progestins, J. Clin. Endocr. 19:1369-1380 (Nov.) 1959.

26. Grumbach, M. M.: Some Aspects of the Pathogenesis of Anomalies of Sex in Man, Pacific Coast Fertility Society, Las Vegas, Nev., Nov. 12, 1960.

27. Pincus, G.; Rock, J., and García, C.-R.: Field Trials with Norethynodrel as an Oral Contraceptive, Proceedings of the Sixth International Conference on Planned Parenthood, New Delhi, India, Feb. 14-21, 1959, pp. 216-230.

28. García, C.-R., and Pincus, G.: Hormonal Inhibition of Ovulation, Investigators' Clinical Report, Nov. 5, 1962.

29. Demars, R.; Blais, J. A., and Pretty, H.: The Use of Norethynodrel in the Treatment of Rheumatoid Arthritis, presented at the annual meeting of the American Rheumatism Association, Chicago, June 21-22, 1962.

30. West, G. H., and Perry, G. R.: Effect of Enovid and Norlutin on Some Liver Functions, Investigators' Clinical Report, 1960.

31. Groff, D. N.: Suggestion for Control of Epilepsy (Letters to the Editor), New York J. Med. 62:3017 (Sept. 15) 1962.

32. Korengold, M.: Investigator's Clinical Report, May 7, 1963.

33. Saskatchewan Hospital Service Plan Analysis for Patient-Days and Cases, 1957 and 1960.

34. Ochsner, A.: Venous Thrombosis, Postgrad. Med. 31:539-545 (June) 1962.

35. Coon, W. W., and Coller, F. A.: Clinicopathologic Correlation in Thromboembolism, Surg. Gynec. Obstet. 109:259-269 (Sept.) 1959.

36. Parker, B. M., and Smith, J. R.: Pulmonary Embolism and Infarction. A Review of the Physiologic Consequences of Pulmonary Arterial Obstruction, Amer. J. Med. 24:402-427 (March) 1958.

37. Ochsner, A.; Kay, J. H.; DeCamp, P. T.; Hutton, S. B., and Balla, G. A.: Newer Concepts of Blood Coagulation, with Particular Reference to Postoperative Thrombosis, Ann. Surg. 131:652-665 (May) 1950.

38. Long, P. H.: Antibiotics and Blood Coagulation (Correspondence), J.A.M.A. 142:49-50 (Jan. 7) 1950.

39. Cosgriff, S. W.; Diefenbach, A. F., and Vogt, W., Jr.: Hypercoagulability of the Blood Associated with ACTH and Cortisone Therapy, Amer. J. Med. 9:752-756 (Dec.) 1950.

40. Keeney, C. E., and Laramie, D. W.: Effect of Exercise on Blood Coagulation, Circulat. Res. 10:691-695 (April) 1962.

41. Pascuzzi, C. A.; Spittel, J. A., Jr.; Thompson, J. H., Jr., and Owen, C. A., Jr.: Thromboplastin Generation Accelerator, a Newly Recognized Component of the Blood Coagulation Mechanism Present in Excess in Certain Thrombotic States, J. Clin. Invest. 40:1006-1018 (June) 1961.

42. Henstell, H.: Investigator's Clinical Report, March 23, 1962.

43. Henderson, E. S., and Rapaport, S. I.: The Thrombotic Activity of Activation Product, J. Clin. Invest. 41:235-244 (Feb.) 1962.

44. Rapaport, S. I.: Investigator's Clinical Report, April 11, 1962.

45. Sherry, S.: Investigator's Clinical Report, April 11, 1962.

46. Turksoy, R. N.; Phillips, L. L., and Southam, A. L.: Influence of Ovarian Function on the Fibrinolytic Enzyme System: I. Ovulatory and Anovulatory Cycles, Amer. J. Obstet. Gynec. 82:1211-1215 (Dec.) 1961.

47. Phillips, L. L.; Turksoy, R. N., and Southam, A. L.: Influence of Ovarian Function on the Fibrinolytic Enzyme System: II. Influence of Exogenous Steroids, Amer. J. Obstet. Gynec. 82:1216-1220 (Dec.) 1961.

48. Pechet, L., and Alexander, B.: Increased Clotting Factors in Pregnancy, New England J. Med. 265:1093-1097 (Nov. 30) 1961.

49. Egeberg, O., and Owren, P. A.: Oral Contraception and Blood Coagulability, Brit. Med. J. 1:220-221 (Jan. 26) 1963.

50. Sise, H. S.; Moschos, C. B., and Becker, R.: On the Nature of Hypercoagulability, Amer. J. Med. 33:667-678 (Nov.) 1962.

51. Verstraete, M.; Amery, A.; Vermylen, C., and Robyn, G.: Heparin Treatment of Bleeding (Letter to the Editor), Lancet 1:446 (Feb. 23) 1963.

52. Special Report: FDA Report on Enovid, J.A.M.A. 185:776 (Sept. 7) 1963.

53. DeBakey, M.: Collective Review: Critical Evaluation of the Problem of Thromboembolism (John Chalmers Da Costa Oration), Int. Abstr. Surg. 98:1-27 (Jan.) 1954, in Surg. Gynec. Obstet. Jan. 1954.

54. DeCamp, P. T.; Landry, R. M.; Ochsner, A., and DeBakey, M. E.: Spontaneous Thrombophlebitis, Surgery 31:43-54 (Jan.) 1952.

55. Editorial: Post-Operative Venous Thrombosis, Brit. Med. J. 2:2-4 (July 6) 1963.

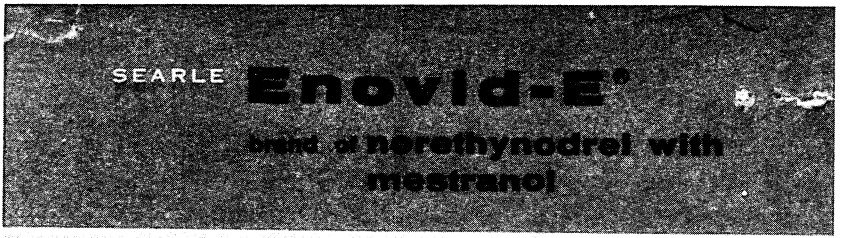
56. Rock, J.; García, C.-R., and Pincus, G.: Synthetic Progestins in the Normal Human Menstrual Cycle, presented at the Laurentian Hormone Conference, Mt. Tremblant, Quebec, Sept. 2-7, 1956.

57. Pincus, G.: Proceedings of a Symposium on 19-Nor Progestational Steroids: Long-Term Administration of Enovid to Human Subjects, Chicago, Searle Research Laboratories, 1957, pp. 105-119.

58. Heller, C. G.; Moore, D. J.; Paulson, C. A.; Nelson, W. O., and Laidlaw, W. M.: The Effects of Progesterone and Synthetic Progestins on the Reproductive Physiology of Normal Man, presented to the American Society for the Study of Sterility, Atlantic City, N. J., April 3-5, 1959.

59. Kupperman, H. S., and Epstein, J. A.: Proceedings of a Symposium on 19-Nor Progestational Steroids: Gonadotropic-Inhibiting and Uterotropic Effects of Enovid, Chicago, Searle Research Laboratories, 1957, pp. 32-45.

G.D. SEARLE & CO.



WHAT IT IS: Enovid-E is a synthetic chemical steroid with the descriptive formula of 17α-ethynyl-17-hydroxy-5(10)-estren-3-one enhanced by mestranol. It is a clinically effective oral progestational substance with added estrogen.

WHAT IT DOES: The principal effect of Enovid-E is to stimulate the endometrium to its luteal or progestational phase early in the cycle with subsequent development of a pseudodecidual endometrium. Menstrual cycles during which Enovid-E is taken are ordinarily anovulatory if medication is initiated on day 5 and continued through day 24 of the cycle. The first post-treatment intermenstrual interval may be prolonged. Spotting or breakthrough bleeding is usually evidence of inadequate daily doses.

INDICATIONS: Contraception or ovulation suppression.

USUAL DOSE: The usual dose is one tablet of Enovid-E daily, further discussed under *Clinical Studies* and *Side Actions.*

HOW TOLERATED: A discussion of contraindications, precautions, and side actions and their control is to be found on pages 7-17.

HOW SUPPLIED: Enovid-E pale pink tablets (containing 2.5 mg. of norethynodrel and 0.1 mg. of mestranol), having a debossed SEARLE on one side and a debossed E on the opposite side, are uncoated and unscored and are available in boxes of 120 and of 600 (6 and 30 Calendar-Packs™ of 20 tablets each), and in bottles of 250.

Senator McINTYRE. Excuse me for interrupting.

Dr. WILLIAMS. Certainly. Thank you.

Obsolescence of statements in advertising, amounting to untruthful misrepresentation, has occurred from time to time, as newer knowledge superseded older. Such were not restricted to the early days of aggressiveness, however, an outstanding example of this practice appeared in the past year. This was at a time when past events and warnings should have made everyone, everyone on the side of promotion, more vigilant than ever to be promptly forthright with physicians and their patients. This relates to the British statistical data, first published in 1967 as preliminary findings on thromboembolism then in 1968 as firm conclusions, about the increased risk of thromboembolism in pill users.

In May 1968 that data was added to the labeling on the pill, all brands, as an emergency measure by the FDA. However, the manufacturers successfully persuaded the FDA to allow a neutralizer in the material.

This has been mentioned before by other witnesses, but I think it deserves some emphasis in this analysis. The impact of the British data was in fact negated, in the minds of many American physicians, by this language:

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, can not be applied directly to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may differ.

Mr. DUFFY. Excuse me, Doctor. Before you leave that statement I would just like to understand something. It was my understanding that Dr. Hellman testified earlier that there is a very strong possibility that the rates of thromboembolism may differ widely between the United States and Great Britain and, in fact, may differ widely among countries and locations. At least, that is what I got from his statement.

How do you justify your previous statement with that of Dr. Hellman?

Dr. WILLIAMS. I cannot justify a lot of things Dr. Hellman says, Mr. Duffy. This has been a matter of concern for many years. If there is a difference, we ought to know it. And they are not to keep relying "may be different." If it is different, let us find out about it. I do not think anything is being done to find out for sure what the incidences are.

Mr. DUFFY. Do you feel that the type of study which is necessary to accomplish this world figure of incidence is an easy thing to do?

Dr. WILLIAMS. No, but because it is not easy does not mean it should not have been done years ago. There are many difficult things in this field, but that is no excuse for delaying them.

In November 1968, Drs. Markush and Siegal of NIH disclosed that their study of mortality data "indicate an association of oral contraceptives with an increase in mortality from diseases of the veins * * *" Although that study was not comparable in technique, it was certainly comparable in conclusion—it did indeed exist. It seems to me it may

not have been included up to the present time because it would have helped debunk sooner than this January some of the language quoted in this "no comparable studies" paragraph.

The results of the Sartwell study, reported in the Second Report on Oral Contraceptives by the Advisory Committee, were known in the spring of 1969, if in fact not sooner, were circulated widely in mimeographed form in August, released to the press in September, but as late as the issue of JAMA for December 29, 1969—which was the last issue I got before I left home—had not been incorporated in the labeling.

This "no comparable studies in the United States" was still there for doctors to read and get whatever reassurance they could get out of it.

Physicians who took solace in the cleverly worded detour around the British data—and there were many who seriously believed that nonsense—were deprived of the comparable American information, unless perchance they read it in the lay press. At the very least, this represents a 5-month delay in disseminating the new information. I submit, gentlemen, it does not take that long to revise the wording or do the new printing required in the advertising for the Journal of the American Medical Association.

The tone of much of the advertising has been to suggest to the doctor that he is indeed in a supreme position to order and manipulate life with his prescription pad.

Let me show you what I mean. On a number of occasions in the Journal of the American Medical Association has appeared this ad for Enovid-E. A photograph of a beautiful child on the lefthand side, and on the righthand side in big bold letters "Just what the doctor ordered."

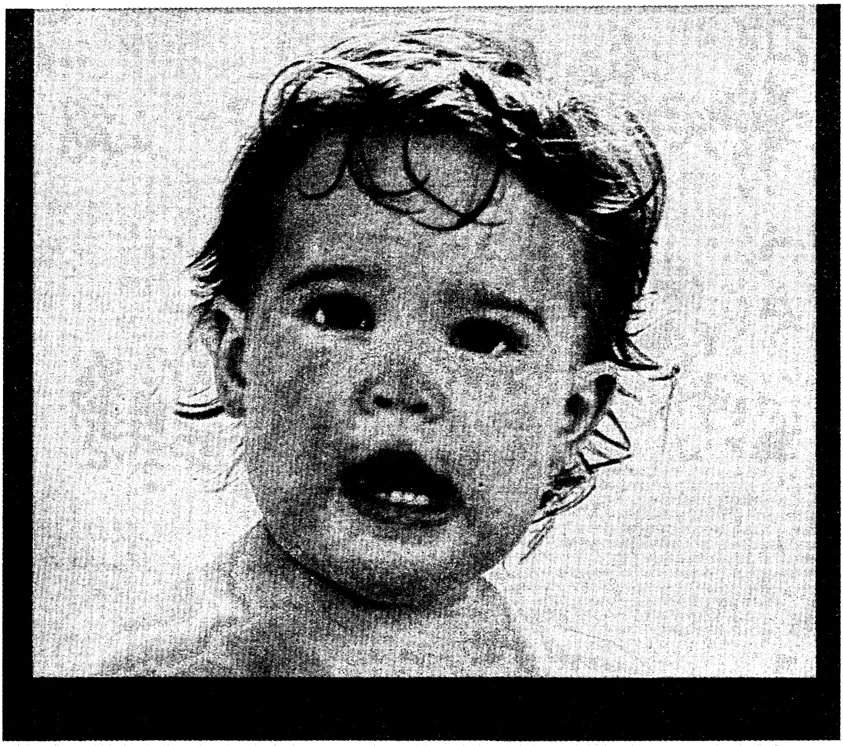
Now, how God-like can you get, gentlemen?

In smaller print, "And spaced just right in the family plan, worked out years before by the physician," and oh, yes, "The baby's parents".

I find it disgusting that this kind of appeal has to be made to American physicians to wheedle them into prescribing the pill for millions of women. If the pill is as good as they say it is, and if it is as safe as they say it is, that kind of advertising would not be necessary.

(The information follows:)

[From J.A.M.A., Dec. 22, 1969, pp. 2198–2199]



Dr. WILLIAMS. But that is not all. The doctor's ego has been pampered so that he may not quite realize he is being treated like a door-to-door salesman for the drug company, who shows him how to get his foot in the door and close the sale.

I will show you what I mean. These are not old ads; these are brand new ones. These are not in the days when they were trying to get it started; this is the day when they are trying to keep it going.

Senator MCINTYRE. What is the date of the ad?

Dr. WILLIAMS. The one I showed you first was December 22, 1969, the journal of the AMA.

I am referring now to the December 1, 1969 issue of that same journal. This one has been repeated many times in journals other than this. On the left-hand side you see a beautiful tender photograph of a new mother with a brand new baby. Now listen to this:

> Now is the time to give her time with Ovulen-21. The new mother needs time to adjust to motherhood, to give her baby all the love and affection he requires. She needs time for her husband and for herself as well, so that she can come to terms with the increased cares and responsibilities now facing her. She needs time to decide when she will have additional children and how many she will have.

Now, on the other side, under a bold heading, "Immediately post partum is the time," we find:

> It is the time when motivation is highest, when a new mother needs expert advice for the future so she can space her children and limit her family.

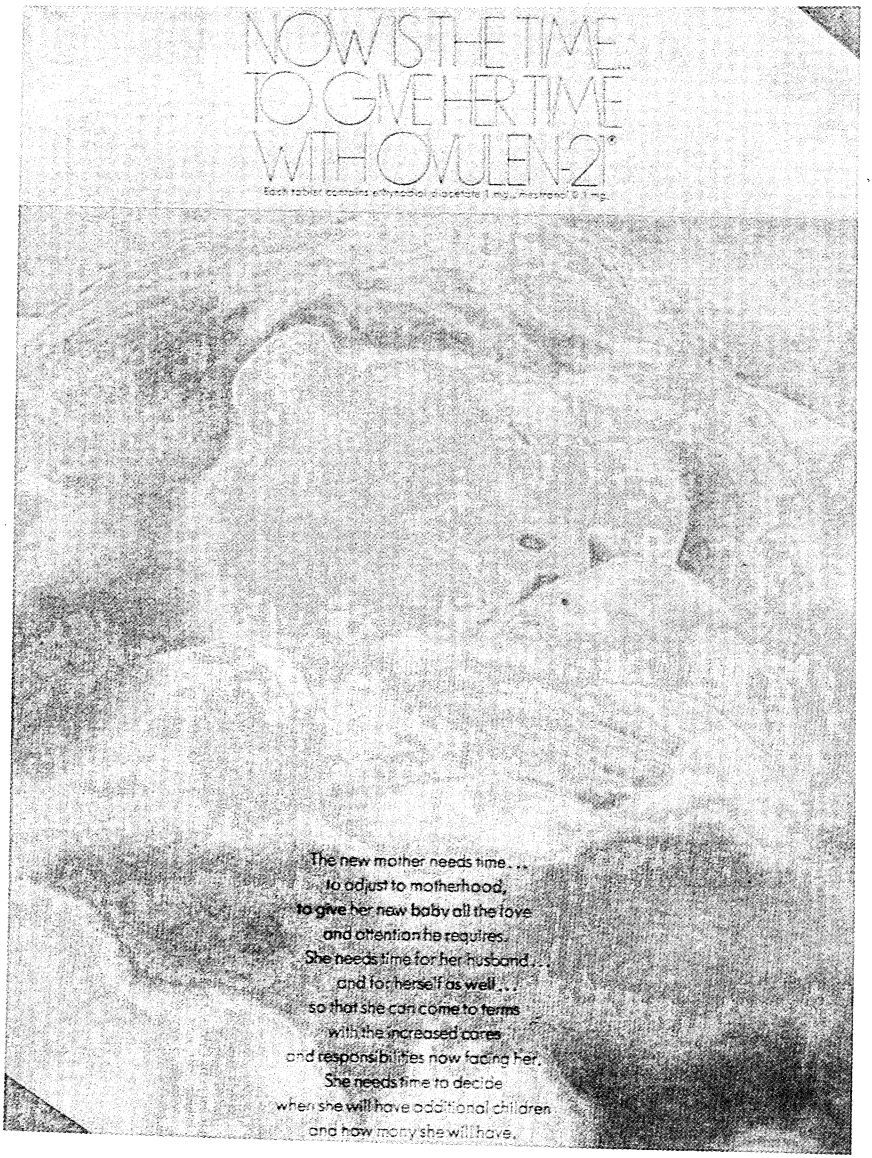
They have the foot in the door and here we close the sale:

> It is also the most opportune time, since she is conveniently present in the hospital, for her to be given both instructions and a prescription.

Catch her when she is unaware; you strike while the iron is hot. And I think it is disgusting and I think American physicians should rally against it. And if they want scientific information, put it in the bold type and not in the fine print that usually takes a magnifying glass to read.

(The information follows:)

[From J.A.M.A., Dec. 1, 1969, pp. 1820–1821]



Senator DOLE. With reference to the advertising, your criticism would apply to all contraceptive devices, not just the pill?

Dr. WILLIAMS. If anything, Senator, is advertised to physicians, professional people like that, I am against it, right. But I have not seen that kind of advertising used very much with other drugs. They use fancy displays; they use catch phrases; but they do not appeal to this side of the doctor so much.

Senator DOLE. Which side?

Dr. WILLIAMS. The side which says go in when the gal is not thinking very well for herself and be sure you leave her a prescription for the pill, because this is when she is most vulnerable.

Senator MCINTYRE. Doctor, you are devoting a good deal of attention to the advertising and promotion of the pill to physicians. You say much of this has been misleading, to say the least. Do you know of any studies or surveys which have been done to determine the extent to which physicians are influenced by advertising and promotion?

Dr. WILLIAMS. I think some have been done, Senator, but I am not closely familiar with them.

Senator MCINTYRE. Do you know the results of any of these surveys and what they show?

Dr. WILLIAMS. No, sir, I do not; I am sorry.

Mr. DUFFY. Doctor, perhaps I could just ask you a question. Prior witnesses before this committee have indicated in response to questions that a doctor is not fulfilling his professional responsibility when he solely relies on promotional material in determining whether or not he is going to prescribe a drug. You, as a doctor and a lawyer, are, I think, in a unique position to determine whether a doctor is or is not fulfilling his professional responsibility. What would you think of a doctor who prescribes any drug just on the basis of promotional material?

Dr. WILLIAMS. Mr. Duffy, doctors are human, thank God, and sometimes we critics of some of them think they are not human enough. But they are subjected to the same kinds of pressures that the housewife is who goes to the market, that the husband is who goes to buy an automobile. Doctors simply do not have time to analyze all of the data and read all the fine print. Occasionally, of course, many of them will. But I am talking about the average man, and I am not deprecating him by saying this. He has human sensitivities. He is influenced by visual aids and audiovisual techniques as much as anybody.

I am just saying that he will pay attention to properly presented scientific information, but he also is likely to be influenced by this kind of advertising. And I suggest to you that if the drug companies did not think it was necessary, they would not be spending the hundreds of thousands of dollars a year to put it out. They would not keep repeating the beautiful picture here of the mother and the newborn baby time and time again at very high rates in the Journal of the American Medical Association if they did not think it got results.

Promotion of the pill has been facilitated through an unusually broad spectrum of activities and attitudes by many people. The principle that "ethical" drugs are not to be promoted to the public has been breached repeatedly and flagrantly. Salesmen were instructed back in June 1961 in a divisional sales manager's memo from the Searle Co., as follows:

"The physician wants to be convinced that Enovid is, one, safe for long-term use."

We shall skip down to the other point I have in my paper—excuse me. I am referring to the wrong one. Let me back up.

Well, I cannot put my finger on the exhibit at the moment, but the quotes are accurate. The salesmen were instructed in what was headlined, "Enovid shopping list"—that is, a checkoff list for the detail men. One was:

Ask pharmacist to suggest to his customers and give them names of doctors in area who write for it. Further down the list he was importuned to do this:

Talk to everyone who will listen and give them the good news that easy child spacing is here.

After the adverse publicity about the pill appeared in August 1962, the salesmen of one company were told in a letter:

"Many people believe that for a certain time period this"—referring to bad publicity—"will definitely slow down the number of requests by patients to physicians for Enovid therapy. As you well know, this is our main and major source of increased and continued acceptance of the drug."

After the adverse——

Senator DOLE. Will you furnish that information for the record?

Dr. WILLIAMS. Yes, Senator. I have it somewhere in my file, but I shall not take time now to put my finger on it.

(The documents referred to follow:)

[From the Searleman, June 1961]

A TIME FOR REAPING—ENOVID 5mg.

(By George J. Striker, Divisional Sales Manager, Chicago Division)

"A Time for Reaping" is the line in a popular hit tune which seems appropriate at this stage of our promotion of Enovid 5 mg. for ovulation control.

Enovid for ovulation control has received tremendous publicity in the lay press and in the most respected medical publications. We also have the help of one of the greatest selling tools we have ever seen; the Enovid Symposium Film.

The time has come when we must ask ourselves, "Are we taking full advantage of this great selling opportunity?"

Check our sales on Enovid and estimate the number of women routinely taking Enovid for ovulation control. Then estimate the potential in our territory and we will find that we have a lot of reaping to do.

It would seem that right now is the time to review our sales story; become more positive in our selling; weed out all the negative points and convince doctors to get patients started on Enovid TODAY.

Let's consider the points that will sell Enovid BIG:

The Physician Selection:

He is probably a G.P. or an Ob. Gyn. specialist seeing young families or mothers.

He is probably recommending some older, less effective method.

He has the practice to start ten, twenty or thirty patients on Enovid.

The Physician wants to be convinced that Enovid is—

1. Safe for long-term use.
2. Effective.
3. Acceptable to his patient; price, convenience, etc.
4. The best method of ovulation control available today.
5. His drug; control of his patient on a month-to-month basis if he desires.
6. Making the role of the physician assume greater importance in family planning according to the wishes of his patients.
7. Giving him a satisfied patient who will appreciate being placed on Enovid.

Let us further convince him with the facts; the proof; the overwhelming endorsement of the top experts in the world today.

Let us weed out unnecessary discussion on:

1. Indications other than ovulation control.
2. Cancer (why discuss it?)
3. Nausea (why discuss it?)
4. Religion (this can be very time consuming and we are interested only in the medical aspect of Enovid).

We have carefully selected the physician for Enovid.

We have taken control of the situation and eliminated as much as possible, unnecessary time-consuming discussions.

We have prepared a positive, convincing sales story, proving that Enovid is effective, safe and the best means of ovulation control available.

We are making each selected call with one objective; Enovid Prescriptions.

Take control; THE TIME FOR REAPING IS NOW.

[From the Searleman, December 1961]

AN ENOVID SHOPPING LIST

The men of the Capitol Division wrote up their ideas on methods to "Keep Enovid Sales Rising". The summary is printed below.

Like the Christmas Shopping List—there are a lot of good ideas listed.

OFFICE CALLS

Call on as many A and B doctors as possible.

Present Enovid to every doctor who has reasonable potential to use, or who should have interest.

Base approach and story on indication with biggest potential for that doctor. If he is using for that, present for next most important use, etc.

Cover conception control use on every call possible, whether primary indication for that doctor or not.

Build story so competitors do not walk off with business on indications other than ovulation prevention.

Individualize story for doctor you are talking with. Be flexible. Determine response during call by questions, leading statements, etc. If he is not in agreement—sell him.

Talk safety where necessary—stress six years "lead time".

Bring out the fact that Enovid is unique—chemically and clinically.

Tell the doctor about the widespread acceptance for conception control.

Cover "bonus" features when taken for ovulation prevention—Definite cycle, predictable bleeding day, slight bleeding when continued, pain free cycle, can vary cycle length.

Back up story with direct quotes, point them out in literature. Don't talk in generalities.

Be complete and thorough on administration. Be sure doctor knows how to use.

Tell the doctor about the economy and high dependability.

Get doctor to recommend regularly for regulation of the menstrual cycle and conception control.

SALES TECHNIQUE

1. Make the presentation interesting.
   a. Say something that catches his attention regarding a particular patient.
   b. Tell what you have heard about Enovid from other doctors, etc.
2. Be enthusiastic but not theatrical.
3. Keep the language simple and try to keep from being overly medical.
4. Make the doctor want to use it.
5. Try to anticipate trouble before it happens and overcome it.

DRUG STORES

Give complete story to pharmacist.

Bring out high sales and profits on repeat business.

Ask pharmacist to suggest to his customers and give them names of doctors in area who write for it.

Leave appropriate literature for his reference.
See that he has adequate stock in best package size.
Learn from pharmacist which doctors are writing it and for what. Use as guide.

HOSPITALS

Emergency room

Find out how they handle bleeders and what they use to treat.
Show them why Enovid is better therapy.
Arrange for Enovid supply through Pharamacy to have available in emergency room to start patients—send them out with scrip for 20–10 mg. tablets.

OBC CLINICS

Initiate usage through residents and key staff men.
Present for problems most frequently seen in clinics—functional bleeding, threatened or habitual abortion, ovulation prevention.
Give story to all doctors and nurses in department.
See that Enovid is adequately stocked in pharmacy.

WHOLESALER

See that stock is adequately maintained in both 5 and 10 mg. tablets in all sizes—insure against shorts.

LITERATURE

Use and leave most appropriate tech. Bulletin each call, and index card.
Use and leave other literature as indicated to support presentation.
Be specific when using literature.

GENERAL

Talk to *everyone* who will listen and give them the good news that easy child spacing is here.

MANAGERIAL MESSAGE

(By Jim Muncaster, Northeast Divisional Sales Manager)

INSTANT SELLING ENOVID

(Not to be confused with Instant Mix Metamucil)

The imperative need for Instant Selling was explained in the communication from Regional Sales Manager Steve Chase in a recent Searleman. Unless you do it NOW there is a high probability, because of pressing competition, you won't have another chance.

As with no other research development, the need for some Instant Selling is apparent with Enovid. You are vulnerable; there is no doubt about it. Competition is coming; there is no doubt about that. When it comes, it will make all previous competition we have faced pale into insignificance. Having captured less than ONE PERCENT of the potential market to date, we have not yet built a brand or product loyalty on the part of the prescriber and consumer to stand us in good stead when the going really gets rough.

A similar product, with only the advantage of a price difference (may it never appear), could make our prize vanish faster than a pickpocket charms a wallet in a crowded subway car. That Enovid is placed in the top spot of succeeding Concentration of Power programs should be an indication of the concern of your management. You are being furnished with unprecedented sales support; the rest is now up to YOU.

We have all heard physicians express fears of chimerical long term effects; carcinogenisis; annoying side actions. In my studied opinion these objections are mere attempts to rationalize the real reason for not prescribing Enovid. You must learn to "read" your doctor. In the Managerial Message delivered a year ago, Stan Farrer asked "What does the doctor really mean when he says . . ." He means, in my opinion, "Give me assurance that Enovid really works".

Let us recall the classic survey of Irving Caplow that appeared in the Harvard Business Review a few years ago. Mr. Caplow stated that physicians prescribed one drug in preference to others for the following reasons, IN ORDER OF IMPORTANCE:

1. Superior efficacy.
2. Safety.
3. Relative lack of side actions.
4. Ease of administration.
5. Price.

These motives hold for Enovid just as well as any other product you are selling.

That poor woman "swollen with child" when unwanted, is a terrible advertisement for the physician among his patients. You now have the most potent convincers to meet this objection, perhaps unexpressed, "will it really work". Give your physician the needed assurance with:

1. Pregnancy Rates by Number of Tablets Missed. Garcia. Pg. 10, Enovid Television Symposium.
2. Fertility Control with Enovid. Table 2, Rock & Garcia, Pg. 17, Research in the Service of Medicine. Vol. 54.
3. Medical Letter #369, van Antwerp, Nov. 8, 1961.
4. Statement by Guttmacher. Pg. 26. Enovid Television Symposium. ". . . Enovid is the best, the most effective Contraceptive known to man."

Plus many other quotes, statements, and charts in your possession.

It is my observation that the most critical point of any sales presentation, and for some reason the one that we have the greatest trouble in handling properly, in asking for ACTION. When we reach the moment of truth, how simple it is to say "Doctor, do you have enough information about, and enough confidence in Enovid to prescribe it regularly in your practice?" Try it next time. If there remain any hidden objections that should bring them out into the open so they can be nailed to the wall.

To close on a biblical note:

"For by the tongue wisdom is discerned; and understanding, and knowledge."

(Ecclesiasticus 4:29)

How about some Instant Enovid Selling?

Dr. WILLIAMS. In a letter dated August 9, 1962, which appeared after the first reports of deaths and thromboembolic disease in users of the pill, the Searle Co. sent a four-page letter to United States and Canadian Searlemen, United States and Canadian Division men, and United States and Canadian salesmangers. On page 3 of that letter we find the words I have just read. Flagrant promotion to the public; flagrant advertising in not so subtle ways, through their detail men, urging people to demand prescriptions. This is not "ethical" drug advertising, never has been, and is not at the present time.

Senator DOLE. I think it might be well to have that entire letter for the record, not just one paragraph.

Dr. WILLIAMS. Oh, yes, the entire letter.

Let me read you the first paragraph of this, Senator. I think it is very interesting.

Excuse me, it will have to be the second paragraph, but it is very short:

"Gentlemen, your exceptional effort to combat an unthinking and sometimes vicious press attack against Enovid and the resultant hysterical fear on the part of thousands of innocent women users has and will continue to earn the gratitude of the respected medical profession. You are to be congratulated. Sometime ago your management foresaw the possibility of such a situation arising. We did not know when; we did not know how; we did not know what about. We only knew that the area of therapeutics as applied to Enovid was a potentially explosive subject."

It goes on to tell about their Bad Press Committee, and if you are interested, Senator, the entire letter is fascinating.

(The letter referred to follows:)

G. D. SEARLE & Co.,
Chicago, Ill., August 9, 1962.

U.S. & Canadian Searlemen.
U.S. & Canadian Divisional Sales Managers.
U.S. & Canadian Regional Sales Managers.

GENTLEMEN: Your exceptional effort to combat an unthinking and sometimes vicious press attack against Enovid, and the resultant hysterical fear on the part of thousands of innocent women users, has and will continue to earn the gratitude and respect of the medical profession. You are to be congratulated.

Some time ago your management foresaw the possibility of such a situation arising. We did not know when; we did not know how; we did not know what about. We only knew that the area of therapeutics as applied to Enovid was a potentially explosive subject. A special "Bad Press" committee was organized, with outlined duties and responsibilities, ready to swing into action if anything should happen. A press release was approved months ago and was ready for immediate release.

At 9:42 A.M. Friday, August 3rd, we were notified of the A.P. release of the British Medical Journal report. Operation "Bad Press' went into immediate effect and the rebuttal in the form of a news release that you have subsequently received was dispatched to the wire services. The battle of words and innuendos continued from the group's operation center through Friday, Friday night, Saturday, Saturday night and Sunday. It still continues.

It has been our contention that we will not take misrepresentation by any group lying down, but will fight back with all resources available to us.

You are to call this number in every instance where letters will not be sufficient. Area code 312-463-2111.

Ask to speak to the following personnel or address your letters to the following personnel as indicated by the subject matter with which you are dealing.

1. Press and Public Relations, James W. Irwin.
2. Physicians and Patients, Dr. Irwin C. Winter.
3. The Drug Trade, William L. Searle.
4. Financial, Kenyon D. Bowes.
5. General, Franklin P. O'Brien.

What are our opinions? What are the plans and programs for the future? (It is possible that by the time this memorandum reaches you this material is outdated. Things are moving that fast.)

Censorship—It should be fully appreciated by you, by the physicians, by your druggists and other members of the health team that since 1938 Pharmaceutical Companies have operated under what could be termed complete censorship by the Food & Drug Administration. A Pharmaceutical manufacturer may only distribute information approved by the Food & Drug Administration.

You have previously received the official news release from the Company. This is not officially approved by the Food & Drug Administration. This is known as exhibit No. 1.

Enclosed is exhibit No. 2. This is the official letter worked out in the Food & Drug Administration's offices that will be sent to 300,000 physicians, pharmacists and other members of the health team. This is our official statement and we may make no statements to the contrary or add additional information that is not encompassed in exhibit No. 1 and exhibit No. 2.

It may be of interest for you to note that this letter was not approved until Tuesday, August 7th (after 3 days of news print hysteria).

The truth—News reports overlook one vitally important fact. The 28 cases of thrombophlebitis and 5 cases of fatal pulmonary embolism did not happen over night. They trickled in over a period of 2½ years. Many cases that may not have been reported will now be reported and our statistics will take on additional meaning.

Exhibit No. 3 is a press release sent out by the Company which denies the rumor established by a representative of the Food and Drug Administration that Searle has not cooperated with them.

Exhibit No. 4 is a reprint from an independent industry publication that we believe explains the story well. (This may not be included. If not, it will be on the way to you shortly.)

We have submitted to the Food and Drug Administration continuously since what is now known as the Philadelphia Conference held April 11, 1962, material regarding "action on blood coagulation" and "incidence of thrombophlebitis" statistics for permission to include in our official brochure. It was not until faced with our personnel at the Food and Drug Administration on Monday, August 6th, that they even recognized that they had received this material. Exhibit No. 5 gives you some of the paraphrasing from this material. The Food and Drug Administration still censors this material to the medical profession and consequently you should not use any part of it.

The consequence—At this writing no one can predict the consequences of our "publicity bath" except to say that in the case of many, many women it has been an extremely frightening and unfortunate occurrence.

Envoid may come through with flying colors and may enjoy even wider acceptance.

Enovid for anti-ovulatory use may be taken off the market or have its claims severely limited.

Enovid may land some place in between the two.

Whatever the consequence, a severe blow has been ruthlessly given to G. D. Searle & Co., to the pharmaceutical industry, to the medical profession and to the confidence of the American people in a system of free medicine.

The medical profession—Your job is with the medical profession—FIRST—LAST—AND ALWAYS. We are determined under any consequences to tell the medical profession the truth as we know it. We may not be able to give all the facts immediately but eventually it will be accomplished.

Our job is not to exaggerate. Our job is to tell the facts as they exist as of the moment we are doing the telling.

The only statement you can make must be based on those official announcements from the Company. You may make no assumption from information coming to you through other sources.

The Medical Profession may find this difficult to understand. Very logically, they expect us to pass on to them every fact in our possession and every opinion and interpretation which we have, and they feel resentful that we cannot do so. The bare fact is that we are only allowed under the regulations of the Food and Drug Administration to relay those statements which have been officially approved by them. We are adhering strictly to these regulations. We think there are a great number of facts which will gradually be relayed as they are cleared. We are doing everything possible to expedite this outcome.

You have told me through your many wires, letters and telephone calls that the medical profession is behind us. They will stay behind us only if we continue to tell the complete unbiased truth. This we must do above all else.

The public—Any causal relationship between Enovid and thrombophlebitis is a far too complicated subject for the non-medical profession segment of the population to understand. They have been fooled badly. They have been scared badly. Many people believe that for a certain time period this will definitely slow down the number of requests by patients to physicians for Enovid therapy. As you well know, this is our main and major source of increased and continued acceptance of the drug.

You can be extremely helpful along these lines in informing us of the public reaction as it takes place from day to day and month to month.

There are many things we can do and I am sure will do regarding the public opinion, but the shrewd guess would be that the scar will remain, even after the healing is accomplished. Only through delicate surgery, with a long recovery period, will it be removed and even then there still may remain memory of the operation.

Our plans—It is going to be a long hard battle which we are determined to win, so long as Enovid continues to prove itself effective and safe.

We will fight for those things that the facts prove to be right.

Now for a few specifics. It is essential that every case of thrombophlebitis or pulmonary embolism that has any possible connection with Enovid be immediately forwarded to the Medical Department, addressed to W. C. Stewart, M.D. We want the complete chapter and verse—the physician or physicians attending and a complete patient history. It is our ethical and moral obligation to turn these case reports over to the Food & Drug Administration for review.

If time continues to prove that there is no causal relationship between Enovid and thrombophlebitis, the physicians and the public must be informed.

If time proves that there is some causal relationship, no matter how remote, the doctors must be informed, because it is his obligation to inform the patient of this remote possibility, so that the doctor and the patient between themselves can decide what is the best course of action.

If time proves that Enovid may be unsafe, you can be sure that your Company would be the first to recognize it and the first to warn against its use. There is nothing new about this statement. We have withdrawn drugs of our manufacture from the market before and I am sure, if it is warranted, we will do it again.

I am firmly convinced that when we are able to view today's events with the calm reason that retrospect offers, we will realize that Enovid must be held blameless. In the meantime, it is important that all of us govern our actions by logic rather than emotion.

Sincerely,

WM. L. SEARLE,
Vice President, Marketing.

Dr. WILLIAMS. Now, the detail man is the foot soldier of the "ethical" drug industry. It is his job to get the doctors' confidence, and to extoll the virtues, and counteract the shortcomings, of his company's products. Although he has done his job well with the pill, overcoming real adversities from time to time, such as in August 1962, he has had a lot of help from the press and other interested parties. Many obstetrician-gynecologists have given him assistance, in part, I think, because they have really enjoyed their exalted position. I am not slamming OB-GYN men. I have a lot of friends in that profession. But this has been a rather peculiar play on their ego, and they have enjoyed their exalted position, created in no small measure by the tenor of promotional efforts, as the ultimate experts about any and everything related to the pill.

I think it is very interesting to point out that this advisory committee formed in 1965 to appraise the dangers of the pill in relation to thromboembolism principally, has been composed of specialists in obstetrics and gynecology and epidemiology, but for some strange reason they had no experts in vascular disease or heart disease or stroke or metabolic disease.

The obstetrician-gynecologist professors have been experts in all of these. I am not deprecating the work of the recent task forces. They have done a very fine job. But it has been a peculiar emphasis. That is all I want to point out here.

Much of the press, as pointed out by Morton Mintz in a fine presentation of the history of reporting of the pill's problems in the Columbia Journalism Review last spring, has refrained from reporting adverse stories while enthusiastically publishing innumerable accounts of its marvels and reaffirmations of its alleged safety. Many newspaper columns and magazine articles have seemed to be little different from paid advertising. These things have been planted over the years too many times to count.

Senator DOLE. Have you discussed this with Mr. Agnew?

Dr. WILLIAMS. It is hard to think of Mr. Agnew and the pill in the same column.

Senator DOLE. He has a reverse complaint. He is not complaining about only the good being reported.

Dr. WILLIAMS. I shall get around to him, if you will be patient with me.

Senator DOLE. I intend to be patient with you, but I hope we can finish by 12:15.

Senator MCINTYRE. I might say, Dr. Williams, that the committee will recess at 12:15 and return at 2:30, for your convenience, because you have been so good to come here and wait. If you do desire, if you have any personal plans and desire to summarize any part of the remaining portion of your testimony in your own interest, that would be fine. However, if you would like to return at 2:30 and resume your testimony, that would be all right.

Dr. WILLIAMS. I would prefer, Senator, to return at 2:30 and not summarize at this time.

Senator MCINTYRE. Go right ahead.

Dr. WILLIAMS. As recently as June 12, 1969, one syndicated physician columnist wrote, in part:

Before contraceptive pills were distributed to the general public, untold control studies were done to be sure of their safety. This is one of the great responsibilities of government health agencies which constantly protect the American people from the "overenthusiasm" for new drugs by their manufacturers.

* * * We must not permit ourselves to be terrified into believing that our health and lives are in jeopardy every time we read scare statistics that have no solid basis in scientific truth.

(The information follows:)

[From the San Francisco Examiner, June 12, 1969]

YOUR HEALTH—"PILL" SCARE STORIES

(By L. L. Coleman, M.D.)

A most terrifying article on birth control pills appeared in a ladies' magazine. It was filled with terrible tales of disabling injuries to the brain and the uterus. I am certain my doctor would never suggest that I take these drugs if they are as harmful as this article says they are. Are we really risking death or permanent injury by taking these pills?

—Mrs. C. W. T.

Dear Mrs. T.: I happened to see the article you referred to and am distressed by the unnecessary fears it highlighted. Unfortunately, some eager writers, with little or no scientific knowledge, find that the greatest impact can be made by emphasizing fear rather than hope in their writing. I disagree completely with this destructive attitude.

Before contraceptive pills were distributed to the general public, untold control studies were done to be sure of their safety. This is one of the great responsibilities of government health agencies which constantly protect the American people from the "overenthusiasm" for new drugs by their manufacturers.

All drugs may have some potential danger. Even the most innocuous drugs can call forth an unusual reaction in the highly sensitive or allergic person. It is with this understanding that your doctor prescribed the birth control pills. The advantages and disadvantages are carefully weighed in the choice of these pills. You can be certain that all these considerations were appreciated by him for you. There are some risks in everything we do. We must not permit ourselves to be terrified into believing that our health and lives are in jeopardy every time we read scare statistics that have no solid basis in scientific truth.

Dr. WILLIAMS. Just 2 months later the second report on oral contraceptives came out, finally giving some "solid basis in scientific truth," with its own scary data. But they are not accused of trying to scare people like those of us who are more interested in getting the truth out than we are in scaring people.

The pro-pill press has repeatedly accepted—apparently on faith—it is hard to really perceive where they get the foundation for this—the assumption, generated by the pill promoters, that it is safe.

Senator DOLE. I wonder if at this point, Dr. Williams, you could supply some of the articles on which you base your conclusion that there is a pro-pill press. I think it would be helpful if you have some stories that have appeared in either a syndicated column or news stories or transcripts from radio or television programs. I think otherwise you have made, again, a statement that we need to have some evidence on.

Dr. WILLIAMS. I shall be glad to furnish it, Senator. I do not have it with me.

I would refer you principally to Mr. Mintz' pair of articles in the Columbia Journal. It is well documented.

Senator DOLE. Is that enough to indict the press as a pro-pill press based on two articles?

Dr. WILLIAMS. He cites a great many news stories and sources. There is indeed, or there has been up until recent days, a pro-pill press.

Senator DOLE. I think it would be helpful, if there is a pattern of an effort, knowing or unknowing, to promote the pill or to report only the good things about the pill, not the bad things, in the press, we should have the evidence, not just a statement.

Dr. WILLIAMS. I shall provide it for you, sir.

Senator DOLE. I assume you have read all these articles?

Dr. WILLIAMS. I have not read them all, no, sir. I live in only one part of the country and I cannot read all the newspapers. But I think it deserves a brief ancedote, if you do not mind, and it will illustrate the problem.

Last September, after I gave a talk to a group of lawyers about the pill, a reporter asked if he could talk to me immediately after, and he was in a hurry because he had a deadline to meet with the San Francisco Chronicle. I laughed and I said, "Well, you are wasting your time; your paper is not going to print anything that is critical of the pill."

He said, "What do you mean?"

I said, "That is the story, that is the history of the Chronicle."

He was skeptical. He went ahead and jotted down his notes. A story did come out in the following day's San Francisco Chronicle.

He called me and he said, "You were right; I had one hell of a time getting my city editor to take anything that was critical of the pill; but I fought with him and I got the watered-down story in."

So it is a reality. It has happened. There are many newspapers that have had a policy against reporting adverse stories about the pill.

Senator DOLE. I think the press is one area and I am not defending the press. I think you have a right to make any comment you wish about the press' reaction, but I think you have made it a very broad statement that there must be a policy for all media to push the pill——

Dr. WILLIAMS. I did not say all the media.

Senator DOLE (continuing). Or to report only favorably about the pill. If this is a fact and you think you can substantiate it, we ought to have all the information. I am a lawyer, too, as you are, and we need the facts, as lawyers know.

Dr. WILLIAMS. I shall be happy to provide it, and I will.

Prominent physicians long identified with pill promotion have actively advanced the cause, often with dogmatic denials of the pill's dangers, often with exaggerated rebuttals of the danger alarms—for example, the pill is safer than pregnancy—and often with irrelevant analogies and misstatements of facts, calculated to obfuscate the issues.

I would like to go back and comment on the statement that the pill is safer than pregnancy. Whenever you hear doctors talk about there are more deaths due to pregnancy than there are to the pill, first of all, they have good data on deaths related to pregnancy. We have very poor, incomplete data about deaths related to the pill. But the vast majority of deaths related to pregnancy, complications of pregnancy, delivery, and the postpartum period, are due to either absent or poor or incompetent medical care. Almost every category of cause of death under pregnancy is related to that. Personally, I find it offensive to hear professors in this specialty in high places comparing or telling you what they tell patients, presumably private patients, about the safety of the pill with that anology. They are saying that if I prescribe the pill for you it has about the same level of danger, or less, than if you went someplace and had a baby without any attention or with an incompetent doctor in attendance. Because the professors in this specialty rarely—it is extremely rare that they lose a patient who may have followed their instructions prenatally and through delivery.

Now, on with some other examples of these exaggerated rebuttals.

Dr. Hellman has been quoted many times as saying "Taking oral contraceptives is about as hazardous as smoking three cigarettes a day"—the most recent clipping I have is the San Francisco Chronicle of Wednesday, April 9, 1968.

Mr. DUFFY. Do you have others, Doctor?

Dr. WILLIAMS. Do I have others than this?

Mr. DUFFY. That you can submit for the record, indicating that he has made similar statements many times?

Dr. WILLIAMS. Yes, I can. This is headed "What a Specialist Thinks of the Pill." Here is the chairman of the Advisory Committee. He was attending a meeting in San Francisco: "Taking oral contraceptives is about as hazardous as smoking three cigarettes a day." Clearly misleading because Dr. Hellman cannot point to any death in any young 18-year-old who has been smoking three cigarettes a day for 60 days. I can show you several case histories of 18- to 20-year-old women who have died from pulmonary embolism after taking the pill for 60 days.

He went on and said in this same news story, "There is not even scant evidence to show correlation between the pill and cancer." That is a direct contradiction to what members of his own committee have come up with. He may not—it is certainly, at the very least, scant evidence to show correlation.

Mr. GORDON. Dr. Williams, may I interrupt here?

Dr. WILLIAMS. Yes.

Mr. GORDON. In Dr. Hellman's testimony, which he did not read this morning, on page 10, he states:

> Known risks of oral contraceptives have often been compared with those of pregnancy, cigarette smoking, and automobile accidents. Such comparisons are probably irrelevant and contribute little to the evaluation of relative risks.

I just thought you would be interested in it.

Dr. WILLIAMS. Then he agrees that it is irrelevant, and therefore, Mr. Gordon, I have to conclude that when he said it, at least in April 1969, it was for promotional purposes only.

Senator DOLE. I think it might be well to have the entire article in the record. Obviously, these sentences are taken out of context.

Dr. WILLIAMS. The entire article is there, sir.

(The document referred to follows:)

[From the San Francisco Chronicle, Apr. 9, 1969]

"POWERFUL DRUG"—WHAT A SPECIALIST THINKS OF THE PILL

(*By Carolyn Anspacher*)

The birth control pill, increasingly a subject of medical controversy, was given the qualified blessing yesterday of one of this country's leading specialists.

Dr. Louis M. Hellman, chairman of obstetrics and gynecology at the State University of New York and chairman of the Federal Drug Administration's Advisory Committee on Obstetrics and Gynecology, wore only his professional hat in making his assessment.

He said studies have shown that it is ten times more dangerous just to step into an automobile than to take the birth control pills and he added: "Taking the oral contraceptive is about as hazardous as smoking three cigarettes a day."

Here to preside at the opening session this morning of the American Association of Planned Parenthood Physicians at the St. Francis Hotel, Dr. Hellman made no attempt to describe the pill as riskless.

Research, particularly in England, he said, has indicated there are three deaths per 100,000 women who take the pill, and one out of 2000 suffers sufficiently serious blood clotting to require hospitalization.

There is also the nagging worry, he said, that the female hormone estrogen, one of two principal components in the pill, could cause cancer of the cervix. But balanced against the fact that estrogen causes cancer in laboratory test animals, he said, it appears that humans are not so endangered.

"There is not even scant evidence," he said, "to show correlation between the pill and cancer, but because of the animal experiments it has been recommended by the Food and Drug Administration that women on the pill have periodic examinations."

Dr. Hellman said there are about 7 million women in the United States and 15 to 20 million women throughout the world taking oral contraceptives.

"Never before," he said, "have so many taken such powerful drugs for anything, but the control or the prevention of disease, and it poses a problem in epidemiology never known before."

Wide use of the pill, he said, began in 1962 and the final safety results cannot be properly gauged for another four years.

One encouraging signpost, he said, is that the incidence of cervical cancer is going down, and if estrogen were indeed a cancer-producing agent in women taking of the pill, then the graph by now would have begun to rise.

The benign and humorous Dr. Hellman finds public reaction to the pill "very sensible." Absolute safety, he said, is not expected. There are disagreeable side-effects that are topics of common conversation, but the risks are balanced against the benefits derived, he said.

Dr. Hellman said the public should not "hold its breath" waiting for the major scientific breakthrough that will guarantee absolute safety in population control.

"The day-after pill is no good," he said. "The long-active pill that contains no estrogen is under study.

"I have no doubt we will ultimately find a compound that will be injectable and will get rid of estrogen entirely, but it will take time."

Some of the new research now under way will be outlined at today's morning-long symposium on the pill, to be attended by 700 of the Nation's leading authorities.

Mr. DUFFY. Did you say he said it and one has to conclude that he said it for promotional purposes?

Dr. WILLIAMS. I said that.

Mr. DUFFY. In other words, you would suggest by that remark that he is perhaps paid by the drug companies to make this statement?

Dr. WILLIAMS. I did not say that.

Mr. DUFFY. I do not understand what it is you are saying.

Dr. WILLIAMS. I am saying Dr. Hellman and a great many other doctors in high places have aided the promotion of the pill. This is not to say they have been paid by the drug companies. They have had other reasons to want to promote the pill. But the promotion of the pill to the public does indeed involve these facets, and this is what I am going into.

One more point on Dr. Hellman, by the way: On TV the other night and in his testimony this morning, he said a lot of drugs are hazardous. We had 200 aspirin deaths in 1967, he said. This has absolutely nothing to do with the hazards of the pill, or even the inherent hazards in aspirin. Those 200 deaths are children who took overdoses of aspirin. They may take overdoses of a lot of things. Aspirin is the handiest and has nothing to do with the innate basic toxicity when taken in therapeutic doses. It has nothing to do with the risks as a drug. It simply states a figure for poisoning by aspirin. When it is injected into this kind of discussion, I think it is misleading and has been every time it has been brought up.

The technique of counterscare has been employed by some physicians indulging in gross exaggerations. In the December 30, 1969, issue of the San Francisco Chronicle, Dr. Bernard Nathanson of Cornell was quoted in respect to what he called "second time arounders."

They are "girls frightened off the pill by scarce articles who come in for a diaphragm, get pregnant, end up in the hands of an abortionist and come back chagrined and chastened, and decide that the pill is less risky than ending up on some kitchen table."

(The information follows:)

[From the San Francisco Chronicle, Dec. 30, 1969]

BACK TO THE PILL

NEW YORK.—Although oral contraceptives have been in general circulation only since 1961, that's long enough for what one doctor calls the "second time arounders."

Dr. Bernard Nathanson, assistant clinical professor of obstetrics at Cornell Medical College, says "second time arounders" are "girls frightened off the pill by scare articles who come in for a diaphragm, get pregnant, end up in the hands of an abortionist and come back chagrined and chastened, and decide that the Pill is less risky than ending up on some kitchen table."

Other methods of contraception are markedly fallible, the gynecologist points out. "The diaphragm has an inbuilt failure rate of perhaps 10 percent."

Dr. Nathanson says the intrauterine device has a three percent pregnancy rate.

Senator DOLE. Do you disagree with that?

Dr. WILLIAMS. I disagree, Senator, because he did not cite any cases. I do not know any documentation of it except this kind of statement in a newspaper story. I would suggest that this kind of thing be documented and if, in fact, it has happened more than once—which I doubt—then people like Nathanson should come forward and say so, how many times has it happened.

Senator DOLE. I think he also says, frightened off the pill by scare articles. Maybe they have been getting some foreign newspapers, because you have indicated that all of ours are pro-pill.

Dr. WILLIAMS. You say that, Senator?

Senator DOLE. No, I say that you have said all our press is pro-pill. Maybe these women were scared off by stories they read in foreign newspapers.

Dr. WILLIAMS. When I refer to the pro-pill press, I am referring to the segment of the press which has been pro-pill. Not all of the press, by any means, thank God.

Senator DOLE. I did not see that qualification.

Dr. WILLIAMS. I apologize for the omission.

Dr. Kistner said that the pill "is safer than pregnancy" and that "mortality is of the same order of magnitude with IUDs as with the pill."

Yet this morning we heard an explanation for the IUD deaths and the 10 that were indicated to the committee were all related to perforation of the uterus, which Dr. Hellman said could be avoided in many instances, and the peritonitis problem and the deaths that have been involved have been ameliorated by greater care on the part of physicians. This is another example of an irrelevant kind of comparison that does not really shed any light on risks of the pill.

Senator MCINTYRE. Doctor, we shall stop here and recess until 2:30.

(Whereupon, at 12:15 p.m. a recess was taken in the hearing, to reconvene at 2:30 p.m. this same day.)

AFTERNOON SESSION

Senator NELSON. You may proceed.

At the time we scheduled this we neglected to note that the President would be giving the State of the Union Message. We had to interrupt for that. Otherwise I ordinarily go through the noon hour. We have to finish these witnesses today.

Dr. Wynn is from out of the country, and Dr. Goldzieher is from out of town, so if you will summarize.

The full statement, as you know, will be printed in the record. I hate to do that but that is the only way we are going to be able to finish today and I have other commitments later this afternoon so if you could summarize the balance we will print everything in your statement in the record.

STATEMENT OF DR. J. HAROLD WILLIAMS—Resumed

Dr. WILLIAMS. I will do my best, Senator, to summarize it. It is a difficult matter, but there are certain things I will say in addition to the printed statement.

Senator NELSON. All right.

Dr. WILLIAMS. I would like to clarify a couple of points that may have been points of confusion this morning, Senator Nelson. One is to make it perfectly clear on the matter of my role as an attorney in litigation. I no longer have any financial interest nor will I in the future have any financial interest in litigation against pill manufacturers. I did say that I had withdrawn from the cases in which I was associated as counsel, and in doing so I did not retain any financial interest.

Also as to the pro-pill press, I want to make it clear that I was referring to a very small segment of the press, which has been characterized in the past as seeming to favor the pill, and I did not mean the total press by any means at all.

To summarize the promotion——

Mr. DUFFY. Dr. Williams, before you go on let me just clarify this a little further. Did you say you have withdrawn from these cases?

Dr. WILLIAMS. That is correct, Mr. Duffy.

Mr. DUFFY. You have completed all the formalities that are required to withdraw from these cases at this particular moment in time?

Dr. WILLIAMS. No, I have not completed the formality of the paperwork in one case. I will do that immediately after returning to California. I just have not had time.

Mr. DUFFY. Thank you.

Dr. WILLIAMS. Senator Nelson, on page 8 I cite from a June 1961 bulletin that went to Searles salesmen. I will not repeat that, but I would like to have that in the record, and also cite from a December 1961 bulletin going to Searles salesmen which is not mentioned in the statement, and it is these two lines that I wanted to include. This is from a divisional sales manager, and I am quoting:

> We have all heard physicians express fears of chimerical long-term effects, carcinogenesis, annoying side effects, side actions. In my studied opinion these objections are mere attempts to rationalize the real reason for not prescribing Enovid.

Senator, to summarize the matter then of advertising and promotion, there are some other documents I would like to get into the record, and these relate to the first full paragraph on page 9. This is a letter from the Nettleship Co. of Los Angeles, insurance brokers. They insure doctors in the southern California area from malpractice. This relates to a form that they advocate their insured doctors have their patients sign before continuing or initiating prescriptions for the pill.

One statement in this form says, this is the patient now to sign this:

"I am aware that such drugs can cause serious reactions and complications both known and presently unknown."

(The information follows:)

THE NETTLESHIP CO.,
Los Angeles, Calif., May 14, 1969.

Contraceptive Pills

DEAR DOCTOR: Because of the increasing awareness of potential complications from contraceptive pills and because we are already handling lawsuits dealing with some of these complications, we are advising physicians to obtain signed statements from their patients which acknowledge requests for these pills despite awareness of the serious risks involved.

We offer the enclosed form which can be used in most instances.

Sincerely,

JOHN C. ALLEN, *President.*

[Enclosure.]

CONTRACEPTIVE DRUGS

Read Carefully Before Signing!

The prescription for contraceptive drugs on this date and for every refill hereafter is at my request. In making this request, I am aware that such drugs can cause *serious* reactions and complications, both known and presently unknown.

Date: ———— Signature of Patient————————

Dr. WILLIAMS. This is dated May 14, 1969. And a letter from G. D. Searle Co. to doctors in California:

"Dear Doctor"—this is dated June 25, 1969. This is a refutation of the Nettleship Company's advice to doctors to get signed consents.

(The information follows:)

G. D. SEARLE & Co.,
Chicago, Ill., June 25, 1969.

DEAR DOCTOR: Recently certain organizations concerned with malpractice insurance have written to physicians with a suggestion that the patient for whom an oral contraceptive is prescribed sign a form. We have discussed this with a broker for malpractice insurance in California and we believe it will be of assistance to you for G. D. Searle & Co. to comment on this action. The form concerned purports to be an acknowledgement by the patient that she has been advised of the "serious reactions and complications" of using oral contraceptives. However, the use of such a form is probably no substitute for the insertion of careful notes on the patient's record showing the information given to her regarding the actions of this or any other medication that has been prescribed. These notes should be entered at the time of the conference with the patient.

As you know, only a physician may decide whether the patient should have an oral contraceptive and, if so, what she should be told concerning the contraceptive. This discretion must be exercised in accordance with the medical history that she supplies, the physician's determination of her physical condition, and the impact he feels such information will have on her well-being and her best interests. This requires explanations which vary for each patient, depending on the findings and expectations.

Consent to use OVULEN® or ENOVID® can best be obtained in this discussion between the physician and his patient. The evidence relating to this consent should be contained in the patient's record. It is questionable whether a signed form such as has been suggested adds anything to proof of such consent.

We are enclosing in this letter the prescribing literature on OVULEN and ENOVID (in this literature discussed in detail are all contraindications, warnings, precautions and side effects) and also the booklet, *Planning your Family*, which may be given to patients, if you desire. This booklet is made available for the purpose of assisting you, by presenting important information about OVULEN, including an effort to cover major contraindications, warnings and precautions in laymen's language. In the event you decide to present this booklet to your patients we suggest that you note this fact on their records and, along with anything else that was said to them regarding the drug. This practice has been discussed with the Nettleship Company and they heartily approve.

You may obtain additional complimentary copies of the booklet from your Searle representative or from G. D. Searle & Co.

Sincerely,

WILLIAM L. SEARLE,
Vice President, General Manager.

Dr. WILLIAMS. Then dated July 1969 is a special report of the California Medical Association News, and this document is in support of the G. D. Searle position that doctors do not need to get signed consents but they should pass out little leaflets which were being offered by the CMA to its members.

(The information follows:)

[From the California Medical Association News, July 1969]

SPECIAL REPORT—INFORMED CONSENT REGARDING "THE PILL" AND NEW DRUGS

In prescribing certain drugs, it is prudent for the physician to give the patient information on the advantages and disadvantages of the medication. This is especially true when patients request the oral contraceptive, popularly known as "the pill." Because of the sensational publicity relating to possible side effects from the pill, we know from past experience in other similar situations that serious patient questions may arise out of real or fancied effects from use of the pill.

CMA has prepared two *Health Tip* articles: one devoted exclusively to the pill, and the other entitled "*How Does Your Doctor Know When a New Drug Is Safe?*" The two articles are available in quantity through CMA and are reprinted below. It is suggested that each physician consider giving the two articles to every patient seeking a prescription for the pill—and in addition, the physician should make an entry in the patient's record of the delivery of the articles. In this fashion, "informed consent" could occur without the physician being required to be a lecturer but with the explanation to the patients being uniform and being done in a friendly, understandable manner. The dissemination of this data by the physician with the corresponding entry in the patient's record has a relationship to the continuation of the physician-patient rapport. The importance of an entry in the patient's record of whatever information you give cannot be overemphasized.

The two articles reprinted here may be ordered in quantity for this purpose at nominal cost from CMA Health Tips.

WHAT YOU SHOULD KNOW ABOUT "THE PILL"

Women who are taking oral contraceptives—generally referred to as "The Pill"—as a method of birth control do so only under medical supervision, and their doctors usually explain to them at the outset that they may anticipate certain side effects, especially in the first months of use.

From time to time, newspapers and magazines carry sensational articles disclosing "new" revelations of dangers which might be associated with the use of the pill, and the peace of mind of millions of women is shattered. Patients may all to readily forget the careful instructions and reassurances they received from their doctors, and react with panic.

Here are some things doctor *do* know and do *not* know about the pill— at this time.

OUR BEST KNOWLEDGE—AT THIS TIME

It is important to remember, first of all, that the pill has been authorized for use only since 1956—that is, only 13 years. It has been in widespread use only since 1961. This means that no woman has taken the pill through the entire span of her reproductive life—from age 14 to age 50. In other words, what your doctor tells you about the possible risk of taking the pill represents the best that is known to medical science at this time. It is not yet known whether years of taking it might produce adverse effects which are not now anticipated. It is impossible, at this time, to know what the genetic effects of the pill might be on future generations, however in the best opinion of most doctors, the pill is safe. These medications are the subject of continuing study and observation, and if any results in the future modify the opinions of doctors, they will share that information with their patients.

What, then, can you believe about the effects of the pill?

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TEMPORARY DISCOMFORT

First, it is true that the pill produces a variety of minor discomforts among women who use it. It should be remembered that the pill acts on the hormonal system, bringing about endocrine changes similar to those which occur during a normal pregnancy. It is logical, therefore, that many of the discomforts which accompany some pregnancies also may accompany the use of the pill. For example, many women using the pill (and many pregnant women) experience nausea and vomiting. Some find that they develop some pigmentation of the skin; other develop acne (On the other hand, many doctors find the pill very effective in *clearing up* acne.) There is sometimes an excessive amount of vaginal mucous secretion among women taking the pill. Others may experience weight gain. In a certain percentage of women there are emotional effects associated with hormonal changes, whether brought about by pregnancy or by use of the pill. These emotional responses may include depression or decreased or increased sexual drive.

These are all temporary changes. They are not serious or threatening. If they are caused by pregnancy, they disappear when the pregnancy is completed and

if they are caused by the pill, they disappear when the pill is discontinued. However, in most cases, the discomforts last only for a few months and the woman prefers to "wait it out" and if her doctor concurs, she continues to take the pill. Sometimes a change of dosage, under medical supervision, relieves the symptoms.

One side effect of the pill does call for treatment. Yeast vaginitis occurs in about 30 percent of the users, which is approximately the same incidence as in pregnant women. This inflammation is not a serious health problem, and it responds well to treatment. Sometimes the treatment can be administered without even discontinuing the use of the pill.

IS "THE PILL" DANGEROUS?

What about rumors of more serious complications resulting from the use of the pill?

The relationship between the pill and cancer has been the subject of many studies. To the best of current knowledge, the pill does not cause cancer of the breast, the cervix, or the body of the uterus. Cervical "*Pap*" smears done on patients who are taking the pill have shown that sometimes there are tissue changes, but there has not been evidence of the development of cancer. Every woman on the pill should have the *Pap* test done regularly; if her doctor finds any hint of abnormality, he will advise her whether or not to discontinue the pill.

Does the pill cause sterility? About 80% of women who are on the pill get pregnant within three months of discontinuing its use when they are ready to have a child. Those who have a difficult time getting pregnant are probably those who were relatively infertile before they started to take the pill.

Does the pill cause malformed babies? The only instances of this have occurred when a woman continued taking the pill *after* she was pregnant. Doctors agree that the pill should not be taken by women during pregnancy.

Finally, what about blood clotting? Here medical opinion seems somewhat divided. Extensive studies have been conducted in both this country and England, and British physicians in recent years have questioned the complete safety of the pill in this respect. This situation is being carefully watched, but medical spokesmen point out that a certain number of all women develop a blood-clotting disease, whether they use the pill or not and that this disease tends to be a complication of pregnancy. In other words, the same women who might develop blood clots while taking the pill might also have developed them during pregnancy. A review of many studies of cause-and-effect relationship between the pill and blood clotting, published in the Journal of the American Medical Association of Feb. 10, 1969 revealed only one case of this disease in 27,000 women-years of pill-use (in other words, one case in 2,700 women using it for a period of 10 years). To sum up our knowledge to date, a risk does exist but it is small, unpredictable, and much less than that involved in a pregnancy.

"THE PILL" AND YOU

The pill, like every other powerful drug, has different effects on different users. Some women may be particularly sensitive to it, just as some people are sensitive even to aspirin. An individual sensitivity does not always mean that the drug is dangerous. It does mean that the individual patient should discontinue its use.

What should you do about the pill? You should discuss family planning fully with your doctor, including the various methods available. If he prescribes the pill, you should follow carefully his instructions concerning its use. Tell him promptly about any changes in yourself which you may notice after you start taking the pill. Go back to him for checkups as often as he advises.

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HOW DOES YOUR DOCTOR KNOW WHEN A NEW DRUG IS SAFE?

In recent years, medical science has made impressive headway in developing new drugs that either prevent or treat diseases which were once life-threatening. Among these achievements have been vaccines, antibiotics, and the cortisone drugs—to cite those which are most widely known. But each step along the way toward controlling disease has been taken slowly and carefully; the process is a painstaking one. Only after a new medication has proved itself through clinical trials will it be licensed for widespread use.

Even after a drug has been authorized as acceptable for use by practicing physicians throughout the country, there always remains some risk in this use. Not all patients react in exactly the same way, and what is entirely safe for one may produce adverse reaction in another. A drug which is highly potent in the treatment of disease is always suspect of causing occasional adverse effects in some patients. Even such a life-saving drug as penicillin can be dangerous for some patients, as some foods are not tolerated by some people.

In giving drugs to patients, the physician takes the responsibility for being familiar with all experimental work which has been done with the drug. Whether the drug is new, or tried-and-true, he does not give it indiscriminately. He prescribes only what he thinks will benefit the patient—the beneficial effect far outweighing possible, but very small, risk. Finally, he will continue to watch the patient to detect evidence of side effects to deal with them appropriately.

When your doctor gives you a prescription for a drug you have never used before, and accompanies it with a discussion of its possible risks, he does not intend to alarm you. He is, rather alerting you. He would not be giving you the medication at all if it were not presumed to be good for you. But he believes that you must share with him the awareness that there might be unforeseen reactions. If the disease being treated is a severe one or has been very resistant to treatment, the patient and the physician are usually more receptive to taking risks. But no significant risk to a patient is ever willingly incurred by the physician. Both physician and patient are, to some extent, at the mercy of the unpredictability of individual responses.

The patient or the parent of the patient should be aware that there is a price, because of these uncertainties, for all improvements in prevention and cure of disease. In explaining potential risks, the physician is seeking the "informed consent" of the patient. The patient must share the responsibility with the physician. When both are aware of this, the course of treatment is likely to go more smoothly.

Dr. WILLIAMS. These four documents, one is printed on two sides, amplify that paragraph on page 9.

Mr. DUFFY. Doctor, before we leave page 8 I am just curious about the last sentence before the first full paragraph:

"Post pill infertility was a worry for manufacturers. Otherwise they would not have alleged its nonoccurence in the early days."

Are you saying that a statement that something does not occur is the equivalent of covering up adverse data? That certainly is a fair implication that one may draw from that statement.

I just wanted to make sure what implication you intended for us to draw from that statement.

Dr. WILLIAMS. This is in the paragraph, Mr. Duffy, in which I am talking about areas of absent, tardy or incomplete research, and the matter of postpill infertility was a point of reassurance by the companies, and that is the implication I want you to draw.

Mr. DUFFY. In other words, adverse data has been covered up?

Dr. WILLIAMS. Either covered up or no effort made to uncover it.

Mr. DUFFY. Thank you.

Dr. WILLIAMS. So, Senator, to summarize on the subject of advertising and promotion, it seems to me that the promotion of the pill has had a great deal of very high placed help in recent days. I think it is strange that the Secretary of HEW, the Commissioner of the Food and Drug Administration, and the newly appointed Deputy Assistant Secretary have all made public statements in the midst of these hearings declaring, I would say safety by decree.

For example, the Secretary said there is no clear-cut evidence that the pill is harmful, and that many women want to keep from having children, and that when many women want to keep from having children the oral contraceptives are the best way to do this.

The Commissioner of FDA said last night on television "There is no reason at this time for women to stop taking the pill," that the emotionalism centered around these hearings will soon fade away and people will not worry about it so much. And if this is not promotion of the pill I do not know what it is.

I think it is not only incorrect medically. I think it is contrary to the facts. I think it is unethical.

The balance of my paper has to do with my analysis of the report submitted by the advisory committee, and I would like to read the last two pages and that will be my summary. This begins at the top of page 14:

The Chairman in his summary states:

Specific risks as well as requisite practices for followup of patients have been detailed in the labeling of all hormonal contraceptives.

Specific risks have not been detailed fully. The labeling still contains serious and misleading ambiguities, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g. retinal thrombosis and optic neuritis.

And:

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: an ovulation post-treatment . . .

This kind of language gives the people who are prescribing the pill something to hide behind if in fact they do not want to believe the facts that have been coming out of these hearings and that are available elsewhere.

As to the "requisite practices for followup" it is interesting to note in the labeling what this includes:

(1) CARCINOGENICITY

Close clinical surveillance of all women taking oral contraceptives must be continued.

If this is not a word of caution and warning I do not know what it is. But the followup finds the cancer after it has occurred and followup does not prevent it. It may prevent its extension but it does not prevent its initial appearance.

(2) THROMBOTIC DISORDERS (INCOMPLETELY LISTED LIMITED TO THROMBOPHLEBITIS, PULMONARY EMBOLISM, CEREBROVASCULAR DISORDERS, AND RETINAL THROMBOSIS)

Should any of these occur or be suspected the drug should be discontinued immediately.

In other words, the followup here relates to the fact after it has happened, and followup does not prevent those things from happening in most instances. It only enables the doctor to find them if and when they do develop.

(3) VISION

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine.

Again followup consists of recognizing it after it happens and does not have anything to do with preventing it from happening.

(4) CANCER AGAIN

The pretreatment and periodic physical examinations should include special reference to the breast and pelvic organs, including a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.

I will not comment further on that.

(5) ENDOCRINE AND LIVER FUNCTION TESTS

If such tests are abnormal in a patient taking the pill, it is recommended that they be repeated after the drug has been withdrawn for two months.

The requisite followup practices if properly and thoroughly done, whenever any of these things are suspected, or whenever they are detected after they happen, I submit, involves an enormous amount of followup cost and expense, the expense of treating these disorders such as vision. A young woman I know had an optic neuritis, sudden complete loss of vision. Fortunately it returned. Her medical costs for this, and incidentally her neurologist, her internist and her ophthalmologist all were in agreement that the pill caused it, the medical costs were $2,500.

Mr. DUFFY. Excuse me, Doctor. Would this have been a litigation in which you were involved?

Dr. WILLIAMS. No, it was not. This is a case brought to my attention a couple of weeks ago as a result of this interest.

(6) FLUID RETENTION

. . . conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction require careful observation.

The implication there I think is that even patients with these disorders may be given the pill if they are carefully observed. I think it is a bad statement. I think it is misleading to doctors generally.

(7) VAGINAL BLEEDING

In diagnosed bleeding per vaginam adequate diagnostic measures are indicated.

And indeed they are.

(8) MENTAL DEPRESSION

Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

And what is left unsaid there is that if a patient develops severe mental depression for the very first time while on the pill, presumably she does not have to be observed carefully. You just wait and see what happens.

(9) DIABETES

. . . diabetic patients should be carefully observed while receiving the pill.

(10) TISSUE SPECIMENS

The pathologist should be advised of the pill therapy when relevant specimens are submitted.

(11) BLOOD PRESSURE

Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Senator Nelson, I think the way this information is accumulating, and the way these requisite followup steps require the most vigilant medical attention, it will not be long until medical students will have to have another year in order to consider the complications of the pill, the way things are going.

What is not included in the "requisite practices for followup" is most interesting.

Mr. DUFFY. Dr. Williams, before you leave that section have you compared this list which you have just brought us with any other list associated with another drug product?

Dr. WILLIAMS. Oh, yes.

Mr. DUFFY. Is there any similarity between this letter say and some other drug products that you might be aware of?

Dr. WILLIAMS. Point for point I do not know.

Mr. DUFFY. A long list of contraindications, symptoms?

Dr. WILLIAMS. Sure, many drugs have long lists of contraindications.

Mr. DUFFY. So this really is not unusual?

Dr. WILLIAMS. Not unusual but it is unusual, Mr. Duffy, because we are not talking about drugs for control of disease.

Mr. DUFFY. What about tranquilizers? Dr. Kistner showed us something very similar.

Dr. WILLIAMS. I did not think Dr. Kistner really meant what he said when he said he prescribed tranquilizers for people who were perfectly well, and I do not think many doctors do. But it begs the question I think to say that there are other drugs with long lists of contraindications. We are talking about the most extensively used mass medication ever followed.

The doctor is not told that strokes occurring in women on the pill have almost always been preceded by a headache (not necessarily a migraine headache), or that fainting spells may be the signal. He is not reminded that thrombotic disease also includes mesenteric thrombosis (intestines), hepatic vein thrombosis (liver) of which there have been reported fatal cases, he is not reminded that it also includes arterial thrombosis, which may lead to a catastrophe in a leg, for example, and there have been amputations necessitated by that. He is not reminded that coronary thrombosis is also part of this thrombotic disease. He is not reminded that when changes in vision occur, or first signs of stroke appear, it may be too late already. The labeling implies that these catastrophes are generally reversible with cessation of medication. Fortunately many of them are, but there is no way to tell ahead of time.

The Chairman goes on:

When these potential hazards and the value of the drugs are balanced, the Committee finds the ratio of benefit to risk sufficiently high to justify the designation safe within the intent of the legislation.

These potential hazards are real hazards, they do not all materialize into damage, but they are real hazards. They present themselves daily,

constantly in millions of women whose physiologic margins of safety have been narrowed in a multitude of ways.

Dr. Wynn and Dr. Doar were the first to point out the significance of lipid changes and carbohydrate metabolic changes, and I think it is generally agreed by at least many of the experts on both sides of the dispute that the metabolic disease potentials are perhaps the most serious of all as a group, and that doctors are not yet told about the comprehensiveness of this worry and about the ultimate potential danger.

The chairman of this Advisory Committee perhaps with the concurrence of some of the committee, has arbitrarily presumed to decide what is safe for millions of women. He has done so knowing that his information is incomplete, that documentation of dangers of the pill has been growing steadily and cumulatively for 10 years, that the most serious problems may be emerging only now.

In making that declaration of safe, he has known that his language would be utilized to the fullest extent in further promotion of the oral contraceptive drugs. For, regardless of all else in the report, the word "safe" is all the drug companies needed out of it.

That completes my summary, Senator Nelson.

(The complete prepared statement of Dr. Williams follows:)

STATEMENT OF J. HAROLD WILLIAMS, M.D., LL.B.

For almost twenty years I have been a physician, although I have not practiced clinical medicine since 1960. In that year I was admitted to the California State Bar, and have written several books for lawyers and physicians, and have practiced law since that time. My law practice is devoted almost exclusively to representing patient-plaintiffs in malpractice cases. My chief concern is for justice in all aspects of the doctor-patient relationship. I try to perceive intrusions, from any direction and from any source, into that relationship. Trust and respect, which of course should be mutual, between doctor and patient is—or should be—the cornerstone of good medical care.

Drugs are essential to modern medicine, but the power of the doctor's prescription prerogative sometimes is a serious intrusion into the doctor-patient relationship. Indeed, that power is so awesome that, I fear, many physicians do not fully comprehend its ramifications when they put pen to pad. Sometimes the physician is unsuspectingly caught in the middle, between his conscientious desire to serve his patients and intensive promotional pressure by drug manufacturers. The sad saga of The Pill is one of the most phenomenal examples of such an entrapment.

My interest in the safety of The Pill became acute just 14 months ago. At that time, November 1968, I was associated as co-counsel in a lawsuit against a manufacturer of oral contraceptives. As I delved into the subject of The Pill's safety, I was amazed at how much information there was, already in the medical literature, about the dangers of oral contraceptives. By May 1969 the assembled facts and documents, including material not theretofore disclosed to either the medical profession or the public, impelled me to write a book. Hopefully, it might help alert physicians and the public to the Pill's dangers, and it might help avert similar disasters in the future.

As I point out some of the things that have happened in the advertising and promotion of The Pill, please bear in mind that the average practicing physician relies upon the drug companies for much, if not all, of his information about drugs. He may read some of the articles in medical journals which report adverse reactions to certain drugs, but by and large he does not have time, nor is he motivated, to read all journals, to sift the poor articles from the good, and to correlate all the information. Obviously, he cannot repeat the research that has been done. Usually he looks to the most convenient central source of information, the Physicians Desk Reference, a compendium of drug company advertising. He assumes that the drug companies are honest and that the F.D.A. has been a vigilant watchdog to protect him and his patients.

For the purpose of convenience in this discussion, I will use the word advertising in reference to graphic presentations to physicians which are readily indentifiable as commercially sponsored sales messages. By promotion I mean all other communications aimed at promoting the sales, use and acceptance of The Pill by the medical profession and by the public.

Advertising of The Pill to the medical profession has been characterized by many statements that tend to be misleading. For example, in Enovid Bulletin No. 20, published in 1964, under a section headlined "The responsibility of leadership" is this statement:

> . . . few drugs in any category have ever been subjected to clinical tests as exhaustive as those already undergone by Enovid.

The reader was expected, no doubt, to understand that statement as applying to safety as well as to efficacy. In fact, the "exhaustive" testing was applicable to efficacy but not to safety. In that same bulletin:

> In the mass of data now on hand, there is *no* evidence that long-term inhibition of ovulation with Enovid impairs post-treatment fertility. . . .

Again, a statement implying that exhaustive work relevant to the subject had been done.

Ambiguous language has been employed many times to take away the sting from information which should have had a warning impact on the physician. For example, in Physicians' Product Brochure No. 62, printed March 16, 1964:

> There is no direct evidence that Enovid alters the diabetic state. However, in a few instances some degree of difficulty in the management of diabetic patients has been reported in connection with Enovid therapy. . . . They may be expected to return to their pretreatment manageability on discontinuance of the drug.

Obsolescence of statements in advertising, amounting to untruthful misrepresentation, has occurred from time to time, as newer knowledge superseded older. Such were not restricted to the early days of aggressiveness, however; an outstanding example of this practice appeared in the past year. This was at a time when past events and warnings should have made everyone more vigilant than ever to be promptly forthright with physicians and their patients. This relates to the British statistical data, first published in 1967 as preliminary findings, then in 1968 as firm conclusions, about the increased risk of thromboembolism in Pill users. In May 1968 that data was added to the labeling on The Pill, all brands, as an emergency measure. However, the manufacturers successfully persuaded the F.D.A. to allow a neutralizer in the material. The impact of the British data was in fact negated, in the minds of many American physicians, by this language:

> No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be applied directly to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may differ.

In November 1968 Drs. Markush and Siegel of N.I.H. disclosed that their study of mortality data "indicate an association of oral contraceptives with an increase in mortality from diseases of the veins. . ." Although that study was not comparable in technique, it was certainly comparable in conclusion, and American physicians should have been told about it in the labeling. It has not been included, perhaps because it would have helped debunk the language quoted above. The results of the Sartwell study, reported in the Second Report on Oral Contraceptives by the Advisory Committee, were known in the spring of 1969, were circulated widely in mimeographed form in August, released to the press in September, but as late as the issue of J.A.M.A. for December 29, 1969, had not been incorporated in the labeling. Physicians who took solace in the cleverly worded detour around the British data—and there were many who seriously believed that nonsense—were deprived of the comparable American information, unless perchance they read it in the lay press. At the very least, this represents a five month delay in disseminating the new information.

The tone of much of the advertising has been to suggest to the doctor that he is indeed in a supreme position to order and manipulate life with his prescription pad. The doctor's ego has been pampered so that he may not realize he is being treated like a door-to-door salesman for the drug company, who shows him how to get his foot in the door and close the sale.

Promotion of The Pill has been facilitated through an unusually broad spectrum of activities and attitudes by many people. The principle that "ethical" drugs are not to be promoted to the public has been breached repeatedly and flagrantly. Salesmen were instructed:

> Ask pharmacist to suggest to his customers and give them names of doctors in area who write for it.
>
> Talk to *everyone* who will listen and give them the good news that easy child spacing is here.

After the adverse publicity about The Pill appeared in August, 1962, the salesmen of one company were told in a letter:

> Many people believe that for a certain time period this will definitely slow down the number of requests by patients to physicians for Enovid therapy. As you well know, this is our main and major source of increased and continued acceptance of the drug.

The detail man is the foot soldier of the "ethical" drug industry. It is his job to get the doctors' confidence, and to extoll the virtues, and counteract the shortcomings, of his company's products. Although he has done his job well with The Pill, overcoming real adversities from time to time, he has had a lot of help from the press and other interested parties. Many obstetrician-gynecologists have given him assistance as they have enjoyed their exalted position, created in no small measure by the tenor of promotional efforts, as the ultimate experts about any and everything related to The Pill.

Much of the press, as pointed out by Morton Mintz in a fine presentation of the history of reporting of The Pill's problems in the Columbia Journalism Review last spring, has refrained from reporting adverse stories while enthusiastically publishing innumerable accounts of its marvels and reaffirmations of its alleged safety. Many newspaper columns and magazine articles have seemed to be little different from paid advertising. As recently as June 12, 1969 one syndicated physician columnist wrote, in part:

> Before contraceptive pills were distributed to the general public, untold control studies were done to be sure of their safety. This is one of the great responsibilities of government health agencies which constantly protect the American people from the "overenthusiasm" for new drugs by their manufacturers.
>
> . . . We must not permit ourselves to be terrified into believing that our health and lives are in jeopardy every time we read scare statistics that have no solid basis in scientific truth.

Just two months later the Second Report on Oral Contraceptives came out, finally giving some "solid basis in scientific truth," with its own scary data.

The pro-Pill press has repeatedly accepted—apparently on faith—the assumption, generated by The Pill promoters, that it is safe. Personal advice columnists, city editors, science writers and others have adopted, almost without question, the assertion of safety. Sometimes, it seems, they made their own decision that benefits outstripped the risks, regardless of what the latter eventually were shown to be.

Prominent physicians long identified with Pill promotion have actively advanced the cause, often with dogmatic denials of the Pill's dangers, often with exaggerated rebuttals of the danger alarms (e.g. The Pill is safer than pregnancy), and often with irrelevant analogies and misstatements of facts, calculated to obfuscate the issues. For example, Dr. Louis Hellman has been quoted many times as saying "Taking oral contraceptives is about as hazardous as smoking three cigarettes a day," and "There is not even scant evidence to show correlation between the pill and cancer."

The technique of counter-scare has been employed by some physicians indulging in gross exaggerations. In the December 30, 1969 issue of the San Francisco Chronicle Dr. Bernard Nathanson of Cornell was quoted in respect to what he called "second time arounders." They are "girls frightened off the pill by scare articles who come in for a diaphragm, get pregnant, end up in the hands of an abortionist and come back chagrined and chastened, and decide that The Pill is less risky than ending up on some kitchen table." Dr. Kistner said that The Pill "is safer than pregnancy" and that "mortality is of the same order of magnitude with IUDs as with The Pill."

The Pill has been promoted by devious devices which have lessened the impact of bad news on physicians and their prescription buying patients. Medical reports adverse to the safety of The Pill have been suppressed or delayed in many instances, so that there would be time for forgetting between installments.

The "comparable" data on thromboembolism in the United States, discussed above, is but one example. Blow for blow rebuttal articles have sprung up at critical times, such as the one described earlier by Dr. Kassouf, that was authored by Drill and Calhoun of the Searle Company and published in the J.A.M.A.

Promotion has been heightened by another assumption implicit in much of the thinking of some segments of our society. That is that The Pill is the *only* method of contraception worth considering. This has caused many young women to remain ignorant of the alternatives until their "side effects" turned into "complications."

Continued sale and use of The Pill has been aided by the convenient lack of data on numerous fronts. Sellers and promoters of The Pill cannot (or will not) tell us very much about why millions of women no longer take it, yet they strenuously objected when a women's magazine attempted to do so. They have not undertaken any laboratory or clinical research (or at least, have not reported any) aimed at yielding comprehensive proof or disproof of a causal relationship between the Pill and thromboembolism. In the absence of published data on experimental and clinical studies, the statistical correlation is all we have to go on, officially. Language such as "statistically significant association" is much easier to swallow, and much better for the pro-Pill cause, than firm statements such as "The Pill causes thromboembolism." Mental depression has been known to be a "side effect" since the earliest days of The Pill, yet it is only very recently that independent researchers began tying down the breadth and depth of that problem. Its risk and ultimate potential danger are still to be articulated.

Other areas of absent, tardy, or incomplete research have been described by other witnesses. It is sufficient here to say that most, if not all, of the areas of major concern today about safety of The Pill were subjects of concern to the manufacturers, and others in the promoters box—ten years and more ago. One indication of this concern appeared in a June 1961 bulletin to Searle salesmen:

The Physician wants to be convinced that Enovid is:

1. Safe for long term use.

Let us weed out unnecessary discussion on:

2. Cancer (why discuss it?)

Tests of bleeding times and clotting times were done on a few women in the Puerto Rico field trials in 1956 and 1957, but the results and the fact that they were done at all, were not included in the published reports. The implication is clear that somebody intimately connected with those trials was concerned, either about the likelihood there would be clotting problems or that some problems already had arisen at that time. And post-Pill infertility was a worry for the manufacturers, otherwise they would not have alleged its non-occurrence in the early days.

Some of the most potent help for the promoters of The Pill came from one of the largest state medical societies, the California Medical Association. In July 1969 it distributed to its members a Special Report about The Pill, including a reprint of a leaflet designed for patients. The leaflet, "What You Should Know About 'The Pill'" contains numerous errors of fact and many words intended to promote The Pill. Doctors were given the opportunity to order the leaflets in quantity so that they could give them to their patients.

SECOND REPORT ON THE ORAL CONTRACEPTIVES, BY THE ADVISORY COMMITTEE ON OBSTETRICS AND GYNECOLOGY, FOOD AND DRUG ADMINISTRATION, AUGUST 1, 1969

Although much of the content of this report is encouraging evidence that we are, at last, facing up to The Pill's problems, certain aspects of it are cause for concern. The exposition of certain hiatuses in knowledge about worrisome questions of long range dangers has been done with care. Indeed, the report appears to place those problems in sharp focus, chiefly in respect of the uncertainties. The disturbing aspects of the report are the tardiness of its accomplishment, the inconsistencies between Task Force reports and the Chairman's Summary, and details of the Summary.

The epidemiologic study of thromboembolism has been a long time coming. The urgency of such a study was stated by various groups of experts, beginning in 1962 and repeated frequently until 1966, when the Advisory Committee rendered its first report. "The present study was begun in November 1965, in

direct response to this need." (p. 21) It is recognized that such studies cannot be accomplished overnight, four years nevertheless is a long time.

The risk of thromboembolism is stated as 4.4 times that of the non-user. This does not tell the whole story. The statistical studies by Sartwell and the British relate to women who are essentially perfect specimens. Women who had so-called predisposing conditions were excluded from the study. We do not know what the risk of thromboembolism is in women who are in good health when starting The Pill, and who subsequently encounter infection, become traumatized, or are beset with other problems. The general susceptibility of the woman taking The Pill has not been measured, nor, apparently, has any attempt been made to do so. Nothing has been done to try to identify the particularly vulnerable woman. We still do not know how many women are being affected by thromboembolism due to The Pill.

One of the major urgent needs, expressed by the various groups in the past, was for "prospective studies." The Advisory Committee, in its First Report on the Oral Contraceptives, August 1, 1966, recommended:

> III. Support of additional controlled population-based prospective studies utilizing groups of subjects that are especially amendable [sic] to long-term followup, such as married female employees of certain large industries, and graduate nurses.
>
> Although such prospective studies are difficult and require large populations, they may provide the only feasible method to answer the question of a relationship between the oral contraceptives and carcinoma, as well as the effect of these compounds on the growth and development of subsequent offspring.

The Second Report contains the following statement in respect of that recommendation (p. 2):

> Result: A prospective study of the effects of the oral contraceptives on cervical epithelium has been underway since 1967. Other prospective studies of effects of contraceptives on cervical cytology have been initiated *recently.* Corollary studies of possible effects on the breast *will also be* implemented. (italics added)

What happened to the large population studies that were deemed so important in 1966? Why are the corollary studies related to cancer of the breast yet to be started? Proposals for long range prospective studies on large population groups (one of 100,000 women, the other of 50,000), submitted to the F.D.A. pursuant to its request of two research organizations, were rejected by the Committee in early 1967. Apparently nothing is being done in terms of large population studies, yet the need is the same as it has been for 10 years.

The various Task Force Reports which, presumably, comprise the basis for the Chairman's Summary present some conclusions that are difficult, if not impossible, to reconcile with the conclusions of the chairman. Most of the deleterious effects, both established and feared but not *proven*, cannot yet be assigned a risk estimate.

On stroke:

> It is not possible with the existing data to estimate with assurance the magnitude of the increased morbidity and mortality risk of stroke among women using these compounds but it may be in the neighborhood of six-fold judging by findings of Inman and Vessey (18) and Vessey and Doll (30). (p. 58)

What does this mean in terms of numerical risk? One in 300, one in 500, or one in 1000 per year among Pill takers? Does the Chairman suggest that the benefit of pregnancy prevention outweighs this unknown quantity, which concededly is probably a sixfold risk?

As to biologic effects, generally:

> It is clear, however, that oral contraceptives have many varied effects on many organ systems. Indeed, there appears to be no organ system tested that is not affected in some way (p. 69).

With such comprehensive involvement, who knows, or can intelligently estimate, what the risks are?

As to post-Pill infertility:

> While clinical observers agree that most women conceive "promptly" after the discontinuation of oral contraception, valid statistical information is scanty. (p. 71).

How does that fit into the formula? Are women to be reassured by guesswork?

As to the outcome of post-Pill pregnancy:

> Continued study of this *problem* should be undertaken, however, since as noted below, there is evidence from laboratory animals that the suspension of ovulation is associated with fetal anomalies once fertility is restored (p. 71).

Another uncertainty, with serious implications.

Concerning cancer of the cervix:

> * * * the Task Force urgently recommends prospective studies of the effect of sustained oral contraception on the immediate and ultimate response of the cervical epithelium in a carefully observed and representative population of women (p. 64).

If, as the Chairman stated on page 2 of the report, under "Results" quoted above, such a prospective study has been underway since 1967, why is the Task Force recommending that it be started?

And, about cancer of the breast:

> The Task Force recommends appropriately devised retrospective case-controlled studies as well as prospective studies to resolve the problem of an effect of oral contraceptives on the incidence and course of mammary lesions (p. 65).

Does this belong in the risk denominator, or was it just ignored?

On the subject of diabetes:

> Whether prolonged administration of steroid contraceptives can result in exhaustion of the insulinogenic reserve and thus induce diabetes in women who are not generally predisposed has not yet been ascertained (p. 75).

A chilling, damning prospect.

Regarding blood vessels and blood pressure:

> The clinical implications of these changes in the concentrations of angiotensinogen, renin, angiotensin, and aldosterone remain to be elucidated (p. 77).

Concerning blood lipids, possibly related to arteriosclerosis:

> Although changes in plasma lipids and lipoproteins are appreciable following the administration of contraceptive steroids, there is no knowledge of the functional significance of these changes (p. 77).

On kidney and urinary tract effects:

> In proportion to the widespread use of oral contraceptives, remarkably little is known about their effects on renal function. * * *
>
> Ureteral dilatation is the only well-documented effect of oral contraceptives on the excretory system. Such dilatation disappears after medication ceases * * * (p. 78).

Few physicians know about the ureteral dilatation; it is not mentioned in the labeling. Yet many women on The Pill have prolonged or repeated urinary tract infections which may be related to this change.

About the central nervous system:

> No information is available regarding the relation between contraceptive steroids and central nervous system excitability (p. 79).
>
> [re migraine] Evidently, more studies are required to ascertain the true incidence of these phenomena (p. 80).

And about the gastrointestinal tract:

> Studies of the effects of oral contraceptives on the gastrointestinal tract are limited (p. 80).

The thousands of women experiencing cramps or other types of abdominal pain while on The Pill generally are said to have "minor side effects" even though they may be due to peptic ulcer or thrombosis.

The Chairman in his summary states:

> Specific risks as well as requisite practices for followup of patients have been detailed in the labeling of all hormonal contraceptives.

"Specific" risks have not been detailed fully. The labeling still contains serious and misleading ambiguities, such as, "Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g. retinal thrombosis and optic neuritis." And, "Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment * * *."

As to "requisite practices for followup" it is interesting to note in the labeling what this includes: (1) Carcinogenicity: "Close clinical surveillance of all

women taking oral contraceptives must be continued." (2) Thrombotic disorders (incompletely listed as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, and retinal thrombosis): "Should any of these occur or be suspected the drug should be discontinued immediately." (3) Vision: "Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine." (4) Cancer again: "The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals." (5) Endocrine and liver function tests: "If such tests are abnormal in a patient taking The Pill, it is recommended that they be repeated after the drug has been withdrawn for 2 months." (6) Fluid retention: " * * * conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation." (7) Vaginal bleeding: "In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated." (8) Mental repression: "Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree." (9) Diabetes: "* * * diabetic patients should be carefully observed while receiving The Pill." (10) Tissue specimens: "The pathologist should be advised of The Pill therapy when relevant specimens are submitted. "(11) Blood pressure: "Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids."

What is not included in the "requisite practices for followup" is most interesting. The doctor is not told that strokes occurring in women on The Pill have almost always been preceded by a headache (not necessarily a "migraine" headache), or that fainting spells may be the signal. He is not reminded that thrombotic disease also includes mesenteric thrombosis (intestines), hepatic vein thrombosis (liver), arterial thrombosis, coronary thrombosis, and others. He is not reminded that when changes in vision occur, or first sign of stroke appear, it may be too late already. The labeling implies that these catastrophes are generally reversible with cessation of medication.

The Chairman goes on:

> When these potential hazards and the value of the drugs are balanced, the Committee finds the ratio of benefits to risk sufficiently high to justify the designation safe within the intent of the legislation.

These "potential" hazards are *real* hazards, presenting themselves constantly in millions of women whose physiologic margins of safety have been narrowed in a multitude of ways.

The Chairman, perhaps with the concurrence of some of the Committee, has arbitrarily presumed to decide what is "safe" for millions of women. He has done so knowing that his information is woefully incomplete, that documentation of dangers of The Pill has been growing steadily and cumulatively for 10 years, that the most serious problems may be emerging only now. In making that declaration of safe, he has known that his language would be utilized to the fullest extent in further promotion of the oral contraceptive drugs. For, regardless of all else in the report, the word "safe" is all the drug companies needed out of it.

Senator NELSON. Thank you very much. I am sorry we had to interrupt your testimony by the recess and we appreciate your patience in waiting and your taking the time to come here to testify.

Dr. WILLIAMS. Thank you, Senator.

Senator NELSON. Senator Dole?

Senator DOLE. I had an opportunity to question Dr. Williams earlier.

As I understand it, you probably would not prescribe the pill. Is that a correct conclusion?

Dr. WILLIAMS. That is absolutely correct, sir.

Senator DOLE. I think again—and I do not quarrel with what you have said because you apparently have a great amount of experience from the legal standpoint—have you concluded any of these lawsuits before you withdrew as counsel?

Dr. WILLIAMS. No, sir; I did not.

Senator DOLE. How many pending, dollar amounts?

Dr. WILLIAMS. You mean in the Nation?

Senator DOLE. That you were involved in.

Dr. WILLIAMS. I was involved in five, but I do not know that——

Senator DOLE. But none of those were concluded prior to the time you withdrew as counsel?

Dr. WILLIAMS. Oh, no.

Senator DOLE. You have withdrawn from every suit involving the pill?

Dr. WILLIAMS. That is right.

Senator DOLE. I have no further questions.

Mr. DUFFY. Excuse me, I am confused now. Maybe I did not understand what you told me earlier, but have you officially withdrawn from every suit involving the pill?

Dr. WILLIAMS. Yes, Mr. Duffy, except for the one in which I still have to do some paperwork to formally take my name off the pleadings. That is the only one.

Mr. DUFFY. Then you are still counsel of record until you do that?

Dr. WILLIAMS. Yes.

Mr. DUFFY. And you will continue to remain so in the eyes of the court no matter what you say here; is that correct?

Dr. WILLIAMS. Until I get home and get the paperwork accomplished, that is right, but I do not say things like this and then fail to follow through.

Senator NELSON. Thank you very much.

Our next witness is Dr. Wynn, professor of human metabolism, University of London, England.

Dr. Wynn is accompanied by Dr. John Doar.

Dr. Wynn has a distinguished medical background.

We will submit for the record a biographical curriculum vitae.

Dr. Wynn, we appreciate your patience in waiting. We are very pleased that you are able to testify. You are now a consultant to NIH; is that correct?

STATEMENT OF VICTOR WYNN, M.D., M.R.C.P., ST. MARY'S HOSPITAL, LONDON, ENGLAND; ACCOMPANIED BY JOHN WILLIS HAMMOND DOAR, M.D., M.R.C.P., LECTURER IN HUMAN METABOLISM, UNIVERSITY OF LONDON, LONDON, ENGLAND

Dr. WYNN. That is correct.

Senator NELSON. You are not testifying as a consultant, but you are a consultant to the National Institutes of Health?

Dr. WYNN. Yes.

Mr. Chairman, I appreciate very much your invitation to attend this inquiry, and allowing me to bring with me my associate, Dr. John Doar who has worked with me for so many years on this problem.

First, I would like to point out that I am a physician, and an endocrinologist, that I see patients suffering from a wide range of metabolic and endocrine abnormalities, and that Dr. Doar is also a physician with similar interests. That we do laboratory work, and that we have taken considerable interest in the chemical changes induced by drugs including steroids and oral contraceptive medications.

All this is set out in my curriculum vitae which I presume will be included in the record.

Senator NELSON. It will.

(The curriculum vitae relating to Dr. Wynn for inclusion in the record follows:)

CURRICULUM VITAE OF PROF. VICTOR WYNN, MD, MRCP, FRC PATH

Name: Victor Wynn.

Date of birth: October 12, 1920. Melbourne, Australia.

Education: Wesley College, Melbourne, 1930–37; University of Melbourne, 1938–44.

Degrees: MB, BS (Melb.), March 1944; MD (Melb.), 1953; FRC Path. 1966; MRCP, 1966.

Academic Distinction: Nuffield Foundation Travelling Fellowship in Medicine, 1950–1951.

Appointments: House Physician and Surgeon, Royal Melbourne Hospital, 1944–1945; Medical Officer, Australian Army Medical Corps, 1945–48; Research Fellow, National Health and Medical Research Council in Department of Physiology, Melbourne University, 1948–50; Nuffield Fellow in Medicine, St. Mary's Hospital, London, 1950–51; Junior Lecturer in Surgery, Surgical Unit, St. Mary's Hospital, London, 1951–53; Senior Lecturer in Surgery, St. Mary's Hospital, 1953–60 and Hon. Consultant (in Clinical Biochemistry), September 1954–60.

Reader in Human Metabolism, St. Mary's Hospital Medical School, University of London, 1960–1969; Consultant in Human Metabolism, St. Mary's Hospital, 1960–; Civil Consultant in Human Metabolism and Endocrinology, Royal Air Force, 1963–; Civil Consultant in Human Metabolism and Endocrinology, Combined Medical Services of BOAC and BEA, 1966–; Civil Consultant in Human Metabolism and Endocrinology, Air Ministry, 1968; Head of the Alexander Simpson Laboratory for Metabolic Research, St. Mary's Hospital Medical School, 1965–; Professor of Human Metabolism, University of London, 1969.

Committees: Medical Research Council, Steroid Sex Hormones Committee, Ministry of Health, Standing Joint Committee on the Classification of Proprietary Preparations, Section on Metabolism and Diabetes.

Societies: Associations of Physicians of Great Britain and Ireland, 1966; Renal Association; Medical Research Society.

PUBLICATIONS

ELECTROLYTES, BODY WATER AND ACID-BASE METABOLISM

1. The clinical significance of sodium and potassium analyses of biological fluids: their estimation by flame spectrophotometry. (1950). Med. J. Aust.; 812. Wynn, V., Simon, Shirley, Morris, R.J.H., McDonald, I.R. and Denton, D.A.
2. Renal regulation of the extracellular fluid. II. Renal physiology in electrolyte subtraction. (1951). Acta med. Scand. Suppl., 26. Denton, D.A., Wynn, V., McDonald, I.R., Simon, Shirley.
3. Water intoxication. (1954). Lancet, i, 587. Wynn, V. and Rob. C.G.
4. Spontaneous and induced water intoxication in two cases of hypopituitarism. (1955). Brit. Med. J. i, 505. Wynn, V. and Garrod, C.
5. A metabolic study of acute water intoxication in man and dogs. (1955). Clin. Sci., 14, 669. Wynn, V.
6. Water intoxication and serum hypotonicity. (1956). Metabolism, 5, 460. Wynn, V.
7. Variation of plasma electrolyte and total protein levels in the individual. (1956). Brit. Med. J., ii, 582. Fawcett, J. K. and Wynn, V.
8. Water intoxication. (1957). Nutrition, 11, 2. Wynn, V.
9. A method of measuring the pH of body fluid. (1957). Lancet, ii, 1068. Wynn, V. and Ludbrook, J.
10. Observations in man upon the osmotic behavior of the body cells after trauma. (1957). Quart. J. Med., 26, 375. Wynn, V. and Houghton, B. J.
11. The osmotic behaviour of the body cells in man. Significance of changes of plasma electrolyte levels in body fluid disorders. (1957). Lancet, ii, 1212. Wynn, V.

12. Some problems of water metabolism following surgery. (1958). CIOMS Conference on "The biochemical response to physical injury. Semmering, Austria. Wynn, V.
13. Citrate intoxication. (1958). Brit. Med. J., 523. Ludbrook, J. and Wynn, V.
14. Technical aspects of electrolyte study. (1959). Royal Coll. Phys. Conf. on "Clinical effects of electrolyte disturbance", Wynn, V.
15. The clinical significance of blood pH and blood gas measurement. (1959), in "A symposium on pH and blood gas measurement". Ed. R. E. Woolmer, pp. 166–182. Churchill: London.
16. The use of venous blood for pH and carbon dioxide studies. Especially in respiratory failure and during anaesthesia. (1959). Brooks, D. and Wynn. V., Lancet, i, 227.
17. Osmolarity disorders of the body fluids. (1960). Postgraduate Med. J., 36, 70–75, 119. Wynn, V.
18. The determination of magnesium in biological materials by flame photometry. (1961). J. Clin. Path., 14, 403. Fawcett, J. K., and Wynn, V.
19. A new principle applied to the determination of calcium in biological materials by flame photometry. (1961). J. Clin. Path., 14, 463. Fawcett, J. K. and Wynn, V. (also in Proc. Ass. Clin. Biochem., 1961, i, 84).
19A. Osmolarity disorders of the body fluids. Part I. Hypernatraemia. Part II. Hyponatraemia. (1961). St. Mary's Hospital Gaz. Suppl. Wynn, V.
20. Acid base regulation in man. (1961). St. Mary's Hospital Gaz. Suppl. Parts I and II. Wynn, V.
21. Water and electrolytes in gynaecological survey. (1962). Chapter in Text Book of Gynaecology, Ed. Bonney.
22. Problems of osmotic and acid base balance in surgery. II. The acid base balance of the body fluids. (1962). Recent advances in Surgery. Ed. Irvine.
23. Some metabolic problems in the management of renal failure. (1962). Brit. J. Clin. Pract., 16, 273. Wynn, V.
24. The alimentary absorption of some enteric-coated sodium and potassium chloride tablets. (1963). J. Pharmacy and Pharmacol., 15, 123, Wynn, V. and Landon, J.
25. Water and Electrolyte metabolism in Surgery. Chapter in "Scientific Basis of Surgery". (1965). Ed. Irvine. Churchill: London.
26. Potassium chloride and intestinal ulceration. (Letter to BMJ and Lancet.). Lancet, Dec. 11, 1965. BMJ, December 25, 1965. Wynn, V.
27. Renin, Angiotensin, Corticosteroids and electrolyte balance in Addison's disease. Brown, J. J., James, V. H. T., Fraser, R., McCusker, J., Lever, A. F., Robertson, J. I. S., and Wynn V. (1968). Quart. J. Med., 37, 97.

HYPOTHERMIA

28. Electrolyte disturbance associated with failure of metabolism glucose during hypothermia. (1954). Lancet, ii, 575. Wynn, V.
29. The metabolism of fructose during hypothermia in man. (1956). Clin. Sci., 15, 297. Wynn, V.
30. Some metabolis problems during hypothermia and surgery in man. (1960). In "Hypothermia". Ed. K. Cooper and D. Ross. pp. 31–40. Cassell: London.

AMINO ACIDS AND PROTEINS

31. A peptide-like contaminant of filter paper. (1949). Nature, 164, 445. Wynn, V.
32. Observations on the behaviour of protein in paper partition chromatography. (1950). Aust. J. Sci. Res. Series B, 3, 124. Wynn, V. and Rogers, G.
33. Chromatographic observations on nitrogenous constituents of petroleum ether extracts of plasma. (1950). Nature, 165, 768. Wynn, V. and Williams, T. N. W.
34. Digestion of protein in the alimentary canal. (1951). Aust. J. Exp. Biol. Med. Sci., 281. Wright, R. D., and Wynn, V.
35. A comparison of two commonly used 'salt-fractionation' methods for differential plasma protein estimations. (1956). J. Clin. Path., 9, 71. Fawcett, J. K. and Wynn, V.

ANABOLIC STEROIDS

36. A study of the androgenic and some related effects of methandienone. (1961). Brit. J. Med., i, 998. Wynn, V. and Landon, J.
37. Studies of hepatic function during methandienone therapy. (1961). Lancet, i, 69. Wynn, V., Landon, J. and Kawerau, E.
38. The effects of an anabolic steroid (methandienone) on pituitaryadrenal function in the human. (1962). J. Endocrin., 25, 199. Wynn, V. and James V. H. T.
39. The effect of an anabolic steroid (methandienone) on the metabolism of cortisol in the human. (1962). J. Endocrin., 25, 211. Wynn, V. and James, V. H. T.
40. Some clinical studies of anabolic steroids. (1962). Anglo-German Medical Review, 1, 4. Wynn, V.
41. Effects of anabolic steroid methandienone on carbohydrate metabolism in man. Metabolism, 2, 501. (1962). Landon, J., Wynn, V., Cooke, J. N. C. and Kennedy, A.
42. Effect of methandienone on response to glucagon, adrenalin and insulin in the fasted subject. (1962). Metabolism, 3, 513. Landon, J., Wynn, V., Houghton, B. J. and Cooke, J. N. C.
43. The effect of anabolic steroids on blood sugar and plasma insulin levels in man. (1963). Metabolism 10. Landon, J., Wynn, V. and Samols, E.
44. Anabolic steroids and protein metabolism. "Modern Trends in Endocrinology" (1967). Butterworths: London.
45. The anabolic steroids. (1968). Practitioner, 200, 509. Wynn, V.

MISCELLANEOUS

46. Effects of posture on plasma volume and some blood constituents. (1956). J. clin. Path., 14, 304. Fawcett, J. K. and Wynn, V.
47. Xanthoma tuberosum with hypercholesterolaemia and hyperproteinaemia. (1957). Acta dermat. venereol., Proc. 11th. Internat. Congr. Dermat., 2, 132. Mitchell-Heggs, G. B. and Wynn, V.
48. Blood pyruvate concentration measured by a specific method in control subjects. (1962). J. clin. Path., 15, 579. Landon, J., Fawcett, J. K. and Wynn, V.
49. Observations upon the metabolic effects of Atromid. (1963). J. Atheroscler. Res., 3, 361. Wynn, V.
50. Vitamins in Surgery. (1964). In "Clinical Surgery" ed. C. Rob and R. Smith. Butterworths: London.
51. The Porphyrias. (1964). In "Clinical Surgery" ed. C. Rob and R. Smith. Butterworths: London.
52. Metabolic aspects of anaesthesia in emergency surgery. (1965). In "Emergency Anaesthesia" ed. Thornton and Knight. Published: Arnold.
53. Metabolic effects of the steroid antibiotic Fusidic acid. (1965). Brit. Med. J., i, 1400. Wynn, V.
54. Effect of posture on the plasma cholesterol level. (1966). Brit. Med. J., i, 336. Stoker, D. J., Wynn, V., and Robertson, Gill.
55. Metabolic effects of carbenoxolone sodium administration in man. (1967). In "A symposium on carbenoxolone sodium" ed. J. M. Robson and F. M. Sullivan. Butterworths: London.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

56. The adrenocortical response to insulin-induced hypoglycaemia. (1963). J. Endocrin, 27, 183. Landon, J., Wynn, V. and James, V. H. T.
57. Adrenocortical function in chornic malnutrition. (1964). Brit. Med. J., i, 662. Cooke, J. N. C., James. V. H. T, Landon, J and Wynn, V.
58. The adrenocorticotropic effects of a synthetic polypeptide -β^{1-24} corticotropin—in man. (1964). J. Clin. Endocrin., 24, 11, 1206. Landon, J., James, V. H. T. Cryer, R. J., Wynn, V. and Frankland, A. W.
59. The effects of some testosterone derivatives on adrenocortical function in man. (1964). J. Endocrin, 29 ii–iii. James, V. H. T., Landon, J. and Wynn, V.
60. Disorders of the adrenal cortex. (1965). In "Scientific Basis of Surgery", ed. W. T. Irvine, Churchill: London.

61. Adrenal response to infused corticotrophin in subjects receiving glucocorticoids. (1965). J. Clin. Endocrin., 25, 5, 602. Landon, J., Wynn, V., James V. H. T. and Wood, J. B.
62. Observations on some extra-adrenal effects of corticotropin on carbohydrate and lipid metabolism in man. (1965). Metabolism, 14, 10. Stamp, T. C. B., Landon, J. and Wynn, V.
63. Oral and intravenous suppression tests in the diagnosis of Cushing's syndrome. (1965). J. Endocrin., 33, 515. James, V. H. T., Landon, J. and Wynn, V.
64. The plasma sugar, free fatty acid, cortisol and growth hormone response to insulin, and the comparison of this procedure with other tests of pituitary and adrenal function. II. In patients with hypothalamic or pituitary dysfunction or anorexia nervosa. (1966). J. Clin. Invest., 45, 4. Landon, J., Greenwood, F. C., Stamp, T. C. B. and Wynn, V.
65. Endocrine function in patients with untreated chromophobe adenomas. (1967). Quart. J. Med., 36, 357. Nieman, E. A. Landon, J. and Wynn, V.
66. The assessment of hypothalamic-pituitary-adrenocortical function in man (1967). Mem. Soc. Endocrin., 17, 213. Wynn, V.
67. A fundamental defect of adrenocortical control in Cushing's disease (1966). J. Endocrin., 40, 15. James, V. H. T., Landon, J., Wynn, V., and Greenwood, F. C.

EFFECTS OF HORMONES ON METABOLISM

68. Observations on some effects of L-triiodothyronine on carbohydrate and lipid metabolism in man. Stamp, T. C. B., Doar, J. W. H. and Wynn, V., (1969) J. clin. Path., 22, 132–135.
69. Effects of Oral and Intravenous Glucose Loading in Thyrotoxicosis. (1969) Doar, J. W. H., Stamp, T. C. B., Wynn, V. and Audhya, T. K. Diabetes, 18, 633–639.
70. The effects of growth hormone on plasma glucose, NEFA, insulin and blood pyruvate levels during intravenous glucose tolerance tests. (1969) Doar, J. W. H., Maw, D. S. J., Simpson, R. D., Audhya, T. K. and Wynn V. J. Endocr. 45, 137–138.

METABOLIC EFFECTS OF ORAL CONTRACEPTIVES

71. Some effects of oral contraceptives on carbohydrate metabolism (1966) Lancet 2, 715. Wynn, V. and Doar, J. W. H.
72. Some effects of oral contraceptives on serum lipid and lipoprotein levels (1966), Lancet, 2, 720. Wynn, V., Doar, J. W. H. and Mills, G. L.
73. Some metabolic effects of oral contraceptives. Clin. Trials J. (London), 5, 171 (1968) Wynn, V.
74. Blood pyruvate and plasma glucose levels during oral and intravenous glucose tolerance tests in obese and non-obese women (1968). Metabolism, 7, 690. Doar, J. W. H. Wynn, V. and Cramp, D. G.
75. Longitudinal studies of the effects of oral contraceptive therapy on plasma glucose, non-esterified fatty acid, insulin and blood pyruvate levels during oral and intravenous glucose tolerance tests. (1969). Proceedings Conference on Metabolic Effects of Gonadal Hormones and Contraceptive Steroids. Ed. H. A. Salhanick, D. M. Kipnis and R. L. Vande Wiele, Plenum Press, New York-London.
76. Fasting serum triglyceride and cholesterol levels during oral contraceptive therapy (1969). Proceedings Conference on Metabolic Effects of Gonadal Hormones and Contraceptive Steroids. Ed. H. A. Salhanick, D. M. Kipnis and L. Vande Wiele, Plenum Press, New York-London.
77. Studies of venous blood pyruvate and lactate levels during oral and intravenous glucose tolerance tests in women receiving oral contraceptives (1969). Proceedings Conference on Metabolic Effects of Gonadal Hormones and Contraceptive Steroids. Ed. H. A. Salhanick, D. M. Kipnis and L. Vande Wiele, Plenum Press, New York-London.
78. Fasting serum triglyceride, cholesterol, and lipoprotein levels during oral-contraceptive therapy, Lancet, ii 756–760 (1969a).
79. Some effects of oral contraceptive on carbohydrate metabolism. Lancet, ii, 761–765 (1969b).
80. The effects of oral contraceptives on carbohydrate metabolism. (1970). Accepted for publication. J. clin. Path.

81. Serum lipid levels during oral contraceptive and glucocorticoid administration, (1970b). Doar, J. W. H. and Wynn, V. Accepted for publication. J. clin. Path.
82. The effects of obesity, glucocorticoid and oral contraceptive therapy on plasma glucose and blood pyruvate levels. (1970c). J. W. H. Doar and Wynn, V. Accepted for publication. Brit. Med. J. 1.

OTHER PUBLICATIONS FROM THE SIMPSON LABORATORY

1. Cerebral tumour presenting with hypeventilation. (1965). J. Neurol. Neurosurg. and Psych., 28, 317. Lange, L. S. and Laszlo, G.
2. Plasma cortisol response to lysine-vasopressin. Comparison with other tests of human pituitary-adrenocortical function. (1965). Lancet, ii, 1156. Landon, J., James, V. H. T. and Stoker, D. J.
3. Stimulation by glucagon of insulin release from rabbit pancreas in vitro. (1966). Lancet, i, 351. Turner, D. S. and McIntyre, N.
4. The plasma sugar, free fatty acid, cortisol and growth hormone response to insulin. I. In control subjects. (1966). J. Clin. Invest, 45, 429. Greenwood, F. C., Landon, J. and Stamp, T. C. B.
5. Assessment of hypothalamic pituitary function in endocrine disease. (1966). J. Clin. Path., 16, 284, Greenwood, F. C. and Landon, J.
6. Growth hormone secretion in response to stress in man. (1966). Nature, 210, 540. Greenwood, F. C. and Landon, J.
7. Plasma non-esterified fatty acid levels in hypopituitary subjects. (1966). J. Endocrin, 35, 107. Stamp, T. C. B.
8. A new technique for the investigation of the low-density lipoproteins in health and disease. (1966). Clin. Chim. Acta, 14, 812. Stone, M. C. and Thorp, J. M.
9. Effect of glucagon on intravenous glucose tolerance. (1967). Brit. med. J., 4, 145. Turner, D. S., Audhya, T. K., Cramp, D. G., Holdsworth, C. D. and McIntyre, N.
10. New automated method for measuring glucose by glucose oxidase. (1967). J. Clin. Path., 20, 910. Cramp, D .G.
11. Automated enzymatic fluorometric method for the determination of pyruvic and lactic acids in blood. (1968). J. Clin. Path., 21, 171. Cramp, D. G.
12. The fluorometric assay of triglyceride by a semi-automated method. (1969). Anal. Biochem. In the press. Cramp, D. G. and Robertson, Gill.

Dr. WYNN. I appreciate particularly the fact that you have invited me here to give testimony, because I come from another country, Great Britain. As I am sure you are aware, far more women are taking oral contraceptive medications abroad than are taking them in this country, and they are doing so in imitation of the American woman, and they are doing so with the confidence which is inspired by the very high standard not only of American medicine, but also of the American regulating agencies, and especially the Food and Drug Administration.

The women in this country and the women in Great Britain and in Scandinavia and in Australia and in South America have been taking oral contraceptive medications in the belief that they are considered safe by the American Food and Drug Administration, and for no other reason, because they have no other way to assess the safety of this medication.

There is not the slightest point in them going to their own doctors to discuss this issue. Their own doctors do not know, and it is perfectly apparent from the testimony that you have had delivered to you here that doctors are very widely divergent in their opinions.

There are some doctors who believe that the oral contraceptives are so safe that they should be available to all women, that they should be put into slot machines, and that no medical supervision whatsoever

is required. If you think that is a wild statement, I do assure you that such statements have been made in 1969 in my country.

I do assure you that a statement appears in this textbook, which is widely available in Great Britain and in America. It is a Textbook of Contraceptive Practice published in 1969, and acclaimed by members of the Family Planning and International Planned Parenthood Federations as being an extremely good textbook, one of the best.

In this book on page 255 a statement appears that under certain circumstances oral contraceptive medication would be acceptable, if they had several hundred times greater mortality than that which is already understood to be the case with this medication.

This implies that in certain communities at any rate according to these authors, and they are intelligent men, dedicated men, men who have the interests of the world at heart, but according to this statement, the oral contraceptive medication would still be acceptable if something like two out of every hundred women were to die every year of its use, and scores of others to be admitted to hospitals every year of its use, leaving the surviving women to care of those who were hospitalized.

Now in this same book the statement is made that on existing knowledge high blood pressure is not a problem, and no woman should have her blood pressure measured in case she should be alarmed by this procedure.

Now, we heard yesterday testimony from Dr. John Laragh who was the first to identify high blood pressure as an associated abnormality of the use of the oral contraceptive, and he said that in his view women should be examined every 2 to 3 months. How far different can one be? Here are doctors, reputable men praised by their colleagues who recommend that women should never have their blood pressures measured, and another doctor who says that they must have their blood pressure measured 2 to 3 months.

Now, herein lies our great dilemma and I put it to you it is the greatest medical dilemma that confronts us at this moment, the division and the deep division between doctors about the safety and the advisability of the use of oral contraceptives.

Now, it is my purpose merely to try and draw attention to some of those chemical changes which occur as the result of the use of these compounds. At least in this field we do have data. At least in this field we need not speculate. We can present evidence which anyone can inspect, and we have done so.

What we still cannot do with any degree of certainty is to interpret the evidence to you. We cannot tell you in what precise way, in how many years, and in what numbers women are going to have their health impaired by these metabolic changes, if indeed they are going to suffer such disadvantages, but it has always been and it still is and it must remain a condition of medical practice that medication must not be used unless it can be proved to be safe, and that the onus of proof is not on those who are investigating the medication. The onus of proof is on those who wish the medication to be used.

In my statement headed "Metabolic Effects of Oral Contraceptive Steroids" which has been submitted to you, it is somewhat lengthy. It is unnecessary that anyone, unless they have a very special in-

terest in this problem, should read the whole document, and I will try to draw attention to those aspects which in my view are important.

I will refer to the page numbers, and to the various diagrams so that those who have copies of this statement will easily be able to follow the gist of my argument.[1]

The first point I would like to make is this. That when contraceptive medication was introduced, the possibility that the biochemistry, the chemistry of the body would be modified in very many ways was not fully understood.

Now, it is all very well for doctors to say "Of course we understood it. We anticipated it. Pregnancy does the same thing," this is not true. I refer to Dr. Gregory Pincus' book published in 1965 and called The Control of Fertility.

Dr. Pincus, as you know, was a very great man, a great experimenter, endocrinologist, and the originator with others of this form of fertility control. But in his book, which is very comprehensive, he barely refers to the metabolic effects of the contraceptive medication.

Why is this? It is because when the book was published the metabolic effects were either inadequately understood or not understood at all. Now Dr. Doar and I had the opportunity of discussing this point in great detail with Dr. Pincus in the following year. He visited us in our laboratory, and we discussed the metabolic findings which we had made, and it was apparent to us that Dr. Pincus was unaware of a wideranging nature of metabolic intervention which follows nd which must follow from the use of this type of chemical.

When I say these changes occur, I mean they occur in everybody, more in some than in others, but no person entirely escapes from the metabolic influence of these compounds. It is merely that some manifest the changes more obviously than others.

Now, before I discuss the contraceptive medication as such, I want very briefly to refer to my own personal interest in steroids and their effects on metabolism because I believe that this is relevant.

We had in 1953 the introduction of very potent steroids for the control of a certain aspect of metabolism called protein metabolism. These substances were derivatives of the male hormone testosterone and they were called anabolic steroids. We studied these compounds, which were very heavily promoted as the present oral contraceptive. We studied these compounds for a number of years, and we became aware of the fact that although they were anabolic in their effect on protein metabolism, they had very many untoward, that is to say undesirable and even harmful metabolic effects such as the following.

They altered carbohydrate or glucose metabolism.

They elevated the lipids in the blood, the fats in the blood.

They altered the metabolism or the ability of the body to handle other important hormones such as cortisone or cortisol as it should be more properly called, and they were even very effective oral contraceptives, both in men and in women.

My own personal experience of these compounds was that they were harmful. Some of my patients had undesirable clinical effects, such as coronary disease, and when I became aware of this potential it was no time at all before I had all my patients stop taking the medication,

[1] See information beginning at p. 6312.

and I published several papers which are listed in my curriculum vitae dealing with this medication and its harmful and dangerous effects.

Now these anabolic steroids were in fact the forerunner of the oral contraceptives, and it would be true to say that the chemical modifications which the steroid chemists had discovered were useful in producing anabolic steroids were the same modifications which were discovered to be useful in producing the orally active fertility controlling drugs which, of course, are all synthetic chemicals.

Fortunately perhaps for those manufacturing these compounds, when the anabolic steroids had lost their favor, the oral contraceptives were there ready to take their place.

By 1961 and 1962 my interest in anabolic steroids had virtually evaporated. The oral contraceptive was introduced into Great Britain in roughly 1961 and became reasonably widely used in 1962 and 1963.

I was very concerned about this development, and I wrote to the Scientific Section of the Family Planning Association in Great Britain, and I warned them that compounds of this type were bound to have wide-ranging metabolic effects in the body, and they invited me to appear before them, and to discuss this aspect, which I did, and that was the last I heard of the matter.

I waited for a year or so. I waited for others to look into this matter, because oral contraceptives were of no interest to me, not the slightest. I was not a gynecologist. I looked on the scene, at the scene. I realized that fertility control was of vital importance, and I was rather horrified at the prospect of it being engineered in this totally artificial way.

It was only because I could find no one interested in this subject that I decided to investigate it myself, and I had the good fortune to have working with me Dr. Doar, and together we explored the potential of these compounds for bringing about metabolic or chemical changes in the body of the user, and we published our first two papers in 1966.

Now, if you would turn to page 6, on page 6 you will see a diagram which is a conventional glucose tolerance test diagram. We had already realized the basic probability that compounds of the type used to control fertility would impair glucose tolerance, that is to say they would make the body less able to metabolize glucose than normal, and if you study the cure on page 7 you will see the glucose values in the blood during the course of the glucose tolerance curve in a normal group of women and a group of women taking oral fertility controlling drugs.

The curves are different. The curve at the top is abnormal. The glucose tolerance of the women taking the pill was impaired. And using criteria which are generally acceptable, using the criteria of the British Diabetic Association and the criteria of the American Diabetic Association, we came to the conclusion that in about 15 to 18 percent of women using this medication, the degree of impairment was such as to justify the term "chemical diabetes."

Now, what do we mean by chemical diabetes? Do we mean diabetes? The answer is "No, we do not." Chemical diabetes is defined as an abnormal glucose tolerance, and nothing else. Diabetes implies that there is also a clinical manifestation of this abnormality in the terms of, let us say, weight loss, or thirst, or passing a lot of urine, and so forth. The

difference probably resides in the fact that diabetes is a more severe form of disorder than chemical diabetes, but is chemical diabetes insignificant? It is not.

Chemical diabetes is significant, and I will come to this point later on in my testimony.

Now, we made observations of these abnormal glucose tolerance curves other than those that I have reported here. We found reason to suppose that the impairment in glucose tolerance was equivalent to that which would be found in women if instead of taking oral contraceptive medication they were being cortizoned. We are all familiar with what cortizone is. We are all familiar with the fact that cortizone produces metabolic changes, and for reasons which are fairly elaborate need not be gone into, but let me say have never been contradicted.

For reasons which we think are sound we believe the impairment of glucose tolerance in these women was equivalent to the disorder produced by an excess of cortizone in the body, and therefore we were entitled to call this abnormality steroid diabetes.

I will return subsequently to further studies which we carried out in this field. But at the same time, because we felt that the blood fat pattern in the blood might be altered by these compounds, we examined the situation, and we found that in a large number of women, there were abnormalities in the fats circulating in the blood.

Now if you will turn to page 8 you will see a diagram in which there are dots on one side of the diagram over the heading "Controls" and the other side of the diagram you will see triangles over the heading "Mestranolethynodialdiacetate" commonly called Ovulex.

Now the dots are lower than the triangles. The triangles are higher than the dots. What this indicates is that this particular fat which we are measuring, which is called triglyceride, a long name and one need not bother too much about it, the triglyceride in the blood is higher in the women taking oral contraceptive medication than in those not taking it, and substantially higher. At least one-third of the users had triglyceroid values higher than the highest value we found in our control subjects.

Now again what is the significance of abnormal triglyceroid values? I cannot answer that question precisely, but that it does have significance, that I believe, and I will return to the subject later. It has been the subject of a tremendous amount of investigation and discussion amongst biologists of various sorts.

Now, we found not only that the triglyceroid was high. We found that the cholesterol was also higher in women taking the pill although the elevation was small. I am sure that there is no need for me to tell an American audience the significance of having your cholesterol levels elevated, since there is so much propaganda in the press, medical, and lay, indicating the importance of having your cholesterol lower, if you can possibly achieve it.

We also, by carrying out more sophisticated type of analysis, studied the actual nature of the circulating fats. Now there is a long name associated with these. The name is lipoproteins, and I do not wish to dwell on it because it is a chemical problem, a complicated one, but we studied the nature of the circulating life of protein, and we found

that the values that we commonly found in women were modified in the direction more commonly found in men.

In other words, we found an abnormality of the lipoproteins pattern of a type which we find in men. Again what is the significance of this? It all leads one's thoughts in the same direction, and the thoughts are these.

Abnormalities of glucose tolerance, impairment of glucose tolerance, and elevation in lipid value and an alternation toward the male pattern lead one to suppose that there may be a risk of the development of the accelerated development of hardening of the arteries or atherosclerosis as it is more correctly known.

The studies we carried out were called cross sectional in the sense that we had a group of women who were users and another group of women who were nonusers. We decided to repeat these studies using the same women as the controls. We investigated them before they started taking the medication, and then at intervals after the medication had been administered, and on page 10 there is a diagram with quite a number of curves on it. I am only to refer to the two left-hand curves. The one represents the glucose tolerance mean curve, and the one at the bottom on the left-hand side represents the insulin curve.

I have so far not mentioned the insulin.

To be brief, what we found was that the impairment of glucose tolerance which we had observed before, was reproduced in these women, and in addition we found that the insulin levels, the hormones which normally controls glucose metabolism, that the insulin values were higher in these women than when they were users.

Insulin-glucose interrelationships and their interrelationships with fat metabolism and the relationships of these three to the accelerated development of atherosclerosis is one of the main medical topics of our time.

On the following page I show you data relating to what happens to a group of women with abnormal glucose tolerance when the medication is stopped and you see that after an interval of 6 weeks to 3 months, the interval since the medication was stopped, that the glucose tolerance curve returns toward normal when the medication is discontinued, so that at any rate was encouraging.

The abnormalities we observed were potentially reversible. I should add that the abnormalities were quite silent. Patients were not coming to the clinics to say, "I think my triglyceroid is elevated," or "My glucose tolerance is abnormal," and the doctors were not saying to the patients, "We think it is time that you had your blood chemistry measured." It would be totally impractical had they done so.

Now, I am going to skip a little of the testimony, and refer now to a few individual case records. I have not selected these cases with the intention of sensationalizing this data. The data I am presenting to you has been given to the National Institutes of Health, Department of Child Health and Human Development, every year for the past 3 years in extenso; we had a 6-hour meeting with them on Tuesday in which we discussed this type of data also extensively. There is no question that this data has been selected out of a rare group of individuals.

These data can be observed relatively commonly.

Now, the first curve I am going to speak of, because I do not want the Senate subcommittee to be here all night, the first curve is a glucose tolerance curve in a young girl who has been on the oral contraceptive for 2 months, and you see that the dotted line on the left top part of the curve is much higher than the other two lines which represent control observations.

Both the glucose tolerance is impaired and the insulin secretion is higher on medication than off it. That is a classical abnormality which we find in as many as 15 percent of the users, and the young healthy users of this medication.

The second case is very similar, but it shows the more gradual return of the abnormal glucose tolerance to normal as the medication is discontinued first for 6 weeks, than for 3 months.

Then turning the page, to page 16, I want to show you the gradual development not of chemical diabetes, which is a symptomless complaint, but of actual diabetes in a user. The first curve, the first solid line shows the glucose tolerance before oral contraceptive medication, and the insulin values associated with it.

You see the impairment of glucose tolerance, and the change in the pattern of insulin secretion after 3 months of the drug's administration, and when you turn the page further, you find that after a year this patient has developed a substantial abnormality of glucose tolerance, and one which no doctor, no doctor whatever his inclinations about the pill might be, no doctor would look at this data and say these changes are harmless. Every doctor would say this patient must stop the medication, which is what we said, and you see the return of the glucose tolerance to normal within 3 months, within 2 months of stopping the medication.

But the point I am making is this: This woman was symptomless. What would have happened to her had we——

Senator NELSON. May I interrupt a moment, Doctor. There is a roll-call on the floor of the Senate. We will recess for 15 minutes.

(At this point in the hearing a short recess was taken.)

Senator NELSON. We will resume the hearings.

Dr. Wynn, we are sorry we had to interrupt you.

Will you proceed, please.

Dr. WYNN. Mr. Chairman, I was in the process of describing to you——

Senator NELSON. Would you talk a little louder.

Dr. WYNN. Yes. I was in the process of describing to you the changes observed in a young woman who developed quite a substantial alteration in glucose tolerance after a year of oral contraceptive medication such that it was mandatory for this medication to be withdrawn, and when it was withdrawn there was a return to normal metabolic function.

Now case 4 is——

Senator NELSON. May I ask if there is any medical evidence of physiologic damage to a person being exposed to a high-level glucose tolerance situation over a long period of time, Doctor?

Dr. WYNN. There is evidence, and there is also a certain amount of conflict of evidence, and I wonder, sir, if I could return to that very important and critical point later?

Now, case 4 I think is a very important study, because it involves the sort of woman who is likely to require continuous administration of oral contraceptive medication for quite a number of years.

This is a woman with eight children, and she is 37 years old when she was sent to me. She is likely to require careful and effective medication, contraceptive medication, or effective contraception for possibly 10 years, because it is apparent I would have thought, and I would have hoped that she would not want any more children.

She was sent to me because her physician had noticed her blood pressure beginning to rise after the administration of Ovulin for 27 months. We carried out a glucose tolerance curve which you can see on page 13 and it is quite obviously abnormal. That is a diabetes——

Senator NELSON. What page are you on?

Dr. WYNN. I am so sorry, page 18.

It is quite obvious that the abnormality is there, and it is equally clear that when the drug is withdrawn and the patient retested on two separate occasions, that the glucose tolerance is normal.

Now there are other features about this woman which cause concern, at any rate to me. First I mentioned the elevated blood pressure which became normal when the drug was withdrawn. But also this woman at the age of 37 had evidence, electrocardiographic evidence, of having had coronary infarction, a myocardial infarction or coronary occlusion, what is more popularly called a coronary or a coronary attack. This was symptomless.

Whether the medication was implicated in the production of this untoward event we will never know and we can never know.

Now, in case 5 a young girl, a young woman with five children was referred to me because again her blood pressure had been slightly elevated, only slightly. We found that she had very substantial abnormalities of her blood fats, and on page 19 there are two diagrams which studied at leisure will become clear, but quickly let me say that on the left-hand side the triglyceroid value is about three times higher than it ought to be.

After stopping the medication for only 7 weeks the triglyceroid value has returned very substantially toward normal, and after stopping the medication for 11 months the triglyceroid value is in fact normal. The cholesterol changes are seen to the right on the curve, and they show the expected but definite improvement in the value in that it is lower off medication than when on.

Now again another rather disturbing feature about this patient was that on examination of the electrocardiogram, it was the opinion of the cardiac consultant of our hospital that this patient had suffered already a silent pulmonary embolism, that there was no doubt in his mind that she had already had thrombotic events, an embolization into the lungs. So here we have a young woman with thrombosis, embolization into the lung arteries, moderate hypertension induced, presumably, by the medication.

Senator NELSON. How do you reach such a conclusion?

Dr. WYNN. That it was induced presumably by the medication?

Senator NELSON. Yes.

Dr. WYNN. I said presumably, and I think I am entitled to use the word "presumably" in the sense that in Great Britain we consider

that the risks of the medication as far as thromboembolism is concerned is considerably greater in the user compared to the nonuser. But when you look at the triglyceroid values and the lipid values, and when you see much abnormalities, these are associated in some curious way with increased incidence of clotting, so that putting the two together, I think it is a reasonable case, but it cannot be proved, and this I think underlines the great difficulty we have with the contraceptives, that what harm they may do may never in fact be proved, and I make this quite clear in my statement I think on page 3.

Now carrying on, I mention other aspects concerned with the contraceptive medication. I mention, for example, that in Great Britain we are in no doubt that these medications increase the incidence of thromboembolism and thrombotic disorders, and that they bring these about in a way which is not quite clear, but that they affect clotting mechanisms and the behavior of certain important blood particles such as the blood platelets, but I cannot continue with this theme at length, because first of all it is complex, and second, we are running out of time.

On page 22 I refer to the production of high blood pressure which Dr. Laragh, who discovered the incidence of it in the first place, described yesterday.

Now, sir, you asked me the question, "What could these changes mean?" They could mean a lot. They do not necessarily mean a lot. We do not know. We must wait and see. But there is an implication, and the implication is this.

These changes in glucose tolerance and lipid metabolism are commonly found in users of contraceptives. I have given you some idea——

Senator NELSON. You mean in the use of the pill?

Dr. WYNN. Oral contraceptives. Now, when you look at the development of accelerated atherosclerosis, that is to say the development of the hardening of the arteries which occurs in younger people under the age of 50, the literature is enormous on the subject, and I have produced a summary of it for you which I would like to submit and have included in the record of over 70 references taken from the literature, produced in the last 3 years.

It is by no means exhaustive. But the references are to the association between abnormal glucose metabolism, abnormal insulin levels, and abnormal blood lipid or blood fat levels, and the accelerated development of atherosclerosis.

Now I can do no more than this. I can do no more than produce evidence. I cannot produce for you evidence that this abnormality is occurring in women taking oral contraceptives, and the reason that I cannot produce the evidence is that not enough time has elapsed.

We have already heard from other people testifying in relation to cancer that we may have to wait 10 or 20 years before we can sit here and definitely pronounce on the subject, but I do want to say that one aspect of the development of coronary disease and stroke is the abnormal clotting which occurs in the blood.

The hardening of the arteries is only one side of the picture. What causes the arteries to become obstructed is the development of the clot on these damaged arteries. Now, the clotting abnormality already has

been demonstrated at any rate to the satisfaction of the committee set up by your Food and Drug Administration to look into the matter. It has been established beyond any possible doubt in the minds of the British equivalent committee.

So if we accept that there is a clotting abnormality, then we have half of the picture of these clotting disorders already.

In Great Britain and also in the United States we have young women having strokes from abnormal clots in arteries. Abnormal clotting in arteries have been included in other sites, in limbs——

Senator NELSON. Excuse me. May I ask has there been a correlation indicating that those who are taking oral contraceptives have a higher incidence of the abnormality than those who do not?

Dr. WYNN. I am sorry, I did not get that. The abnormality of?

Senator NELSON. You were referring to——

Dr. WYNN. To stroke.

Senator NELSON. To thromboembolism at that moment?

Dr. WYNN. I was referring just now to stroke, peripheral artery disease and coronary disease.

Senator NELSON. Excuse me, is there a correlation between women who are suffering from stroke, atherosclerosis, and the incidence of those who are on the pill vis-a-vis those who are not taking oral contraceptives?

Dr. WYNN. Yes; that evidence is available in the April issue of the British Medical Journal of 1968. The authors of the article are Dr. Devlin and Dr. Vessey. There are other complications as well, and to a considerable extent the data confirm these observations, and I had a conversation with Dr. Sartwell last night in which he expressed as his opinion that the American data confirmed as far as he was concerned the British findings.

I have also the unhappy task of informing you that according to an unpublished British report which has been given to me by the one person best qualified to assess the situation, that there is already a significant increase in the development of acute coronary disease in young women taking oral contraceptives.

Senator NELSON. You say this is an unpublished report. Is it to be published?

Dr. WYNN. This will be published within the next 2 to 3 weeks. So I would like to pass on if I may to the next point. Or rather I should say that I would like to summarize this point that you asked me the significance of this data.

I do not know what the significance of the data is. I repeat this, that I am concerned, and every reasonable physician that I have spoken to on the subject is concerned. The Food and Drug Administration and the experts at the National Institutes of Health are equally concerned. We are not alarmed, and there is no reason why women should be alarmed at the results of my pronouncements.

We are seriously concerned. There is a great deal of difference.

We have to examine this situation. I listened very carefully to your words yesterday, when you were looking at the same proposition: Should we in fact be sitting here, with television cameras, and the world press, to discuss such an important subject?

I have had to ask myself this question, and I have no doubt that you have also seriously asked yourself this question, and I have no doubt about the answer, and the answer is this. We must discuss it. We must discuss it as rational, intelligent beings, as unemotionally as we can, and we must examine the evidence.

If the evidence is there, let us examine the evidence. If the evidence is not there, let us do everything we can to obtain the evidence. But on no account can we put this subject completely behind not an Iron Curtain but something which is substantially much worse.

Now there are other implications in our data. There is a suggestion, and any reasonable physician would accept this, that the changes we have seen, and we have described, could in the end of long-term usage of oral contraceptive medication increase somewhat, by an uncertain amount, the incidence of actual diabetes mielitus, the clinical condition we call diabetes.

Now, I have given in my account as fair a statement on the position as I think I can go. I do not think this risk is very great, but I think the risk is there.

Finally, I would like to conclude with two statements, because this metabolic problem is vaster, far vaster than that which I have outlined to you. It covers every disadvantage ever stated about the oral contraceptive, all the disadvantages of this medication stem from the metabolic changes, whether they be changes in personality, whether they be changes in putting on weight, whether they be changes in skin pigmentation or what have you, high blood pressure.

These are all metabolic changes, and vast numbers of these changes have been identified. And so I could go on at great length, but I do not intend to bore you with this, but I do want to make, if I may, two points.

Dr. Pincus in 1962, and this statement appears on page 28, considered the problem of the justification of the use of contraceptive medication, oral contraceptive medication purely with steroids, purely for the purposes of contraceptives, and he said that if this medication was to be justified, it must meet three criteria, and the criteria quote word for word from his book, or rather from his article:

"The first criterion is the avoidance of any pathological side effect. This must be assured."

We have described pathological side effects, and we have heard others describe such effects.

Second was that "The continuation of normal physiological function must be assured."

There are more than 50 ways in which the metabolic functions of the body are modified, and to say therefore that normal physiological function has been demonstrated in the years of oral contraception is to overlook a very large amount of information.

Finally, "There should be no impairment of subsequent fertility by the medication."

I am in no position to judge this, but I know that this is already a matter for some concern.

Now my final remarks really amount to this. Where do I stand in relation to this medication.

It gives me no pleasure to give such an account on this subject. I derive no satisfaction from having to give a detailed description of events which we all would prefer not to be occurring in women, but it is my duty to do so.

The metabolic changes are there. It is necessary that those with responsibility examine the health of women in such a way that they can detect in good time whether these changes are deleterious or not, and if so what is the order of magnitude of the risks, but there is no time to be lost. Far too much time has already gone by without these relevant studies having been carried out.

I have read today of the decision of the Food and Drug Administration to have regular meetings every 4 to 6 weeks, according to the report in the Washington Post, and I am very well satisfied with that report.

I think you must review the position and review it in detail, and keep it constantly under review, but on no account can we overlook this sort of data.

Thank you.

Senator NELSON. Thank you, Doctor.

(The complete prepared statement and supplemental information submitted by Dr. Wynn follows:)

STATEMENT OF PROFESSOR VICTOR WYNN, M.D., M.R.C.P., F.R.C. PATH. PROFESSOR OF HUMAN METABOLISM, UNIVERSITY OF LONDON, ENGLAND

METABOLIC EFFECTS OF ORAL CONTRACEPTIVE STEROIDS

Mr. Chairman and Members of the Committee, oral contraception as we know it today, may be said to have begun in April 1956 when Dr. Edris Rice-Wray, in collaboration with Dr. Gregory Pincus and others began the large-scale administration of the drug Enovid to healthy women in the fertile age group, residents of the town of San Juan in the island of Puerto Rico. Enovid is still a widely used oral contraceptive, although the strength of the two steroids used, mestranol and norethinyodrel have been substantially decreased in the more modern formulations. The technical efficiency of oral contraceptive medication is not in doubt. What is uncertain is the effect of the medication on the health of the user, especially if the drugs are consumed for several years. I propose to submit to you evidence of the wide ranging changes in the chemistry of the body which oral contraceptives produce. These changes are referrd to as metabolic effects and they were largely unknown when the drugs were first introduced. In his book, "The Control of Fertility" * Dr. Pincus, who may rightly be considered the originator of oral contraception, deals only cursorily with the metabolic effects of the medication. This is not surprising, because although the book was published in 1965, up until that time, very few metabolic studies had been published and some of the original observations were either inconclusive or contradictory. Even now, 14 years after the introduction of oral contraception, opinion is divided as to exactly what are the metabolic effects of this medication and more particularly what are the implications so far as the women's health is concerned.

Before describing the metabolic effects of oral contraceptives, I would like to go back to the period of the 1950s to discuss another but related topic, because it gives insight into what may be considered to be the undesirable effects of the contraceptive drugs, and it gives me an opportunity of explaining how my research in this field originated and how I have come to those conclusions which I shall shortly put before you.

*The Control of Fertility, by Gregory Pincus, 1965, Academic Press, New York and London.

Oral contraceptives, in their most widely used form, are mixtures in various proportions, of two types of synthetic steroid, an oestrogen and progestagen. The female hormones, oestradiol and progesterone, are not active when taken by mouth. This disadvantage can be overcome by modifications of the parent steroid. In each case, the modification protects the steroid from inactivation in the liver, so that if given by mouth it passes through the liver and can therefore reach the target issues in an active form. The idea that steroid hormones could be chemically modified in order to make them active when given by mouth is not new. In 1938 it was found that by adding a methyl radical to the 17 carbon of testosterone, an orally active form of this male hormone could be produced. The compound, methyl testosterone, became a prototype for similar modifications to the other gonadal steroids. For example, it was soon followed by the introduction into clinical practice of the orally active oestrogen, ethinyloestradiol. In this drug, the ethinyl radical is added to the 17 carbon of oestradiol, rendering the parent hormone orally active. At about this time, another interesting discovery was made by the synthetic chemists. It was shown that if the ethinyl radical was added to the 17 carbon of testosterone, the resulting compound (ethisterone) ceased to be a strong androgen, but became quite a potent progestagen. This was the beginning of the use of the testosterone molecule to produce hormonal-like steroids simulating the action of progesterone. The next major discovery in the synthetic sex steroid field occurred early in the 1950s when it was found that by removing the methyl group attached to the 10 carbon in testosterone, a compound with novel characteristics was produced, the 19 nor-steroid. 19-nor-steroids can be used to produce two classes of drugs, namely potent anabolic steroids and very effective orally active progestagens. An anabolic steroid may be described as a compound which retains the protein-building anabolic effects of testosterone but has much reduced virilising action. The orally active progestagens have already been described as mimicking the effects of progesterone. Amongst the earliest of the orally active anabolic steroids exploiting the 19-nor-steroid configuration was Nilevar (17-α-ethyl-19-nortestosterone). Norethynodrel (17-α-ethinylestrenalone) was one of the first of the 19 nor-steroid progestagens. Both of these compounds were synthesised in the research laboratories of G. D. Searle and Company.

My studies of the clinical effects of orally active enabolic steroids started in 1957 and went on for several years. I began hoping to find justification for the claims made by their promotors that these compounds were effective remedies in the treatment of many distressing conditions, especially those associated with protein depletion, debility, cachexia, wasting, osteoporosis, post-operative weakness, steroid induced protein catabolism, and even the infirmity of old age. I found instead, that these compounds seemed to have little clinical usefulness but that they produced many metabolic side effects. These effects have been described in the publications numbered 36 to 45 in my curriculum vitae, which is appended with this statement. I draw attention particularly, to publication No. 44, entitled "Anabolic Steroids and Protein Metabolism" and published in *Modern Trends in Endocrinology*, 1967, by Butterworths in London. This article summarises several years experience of the clinical use of anabolic steroids. We found, for example, that these compounds could impair glucose tolerance, cause plasma cholesterol levels to rise, modify the function of the liver in several ways, alter the metabolism of the adrenal hormone, cortisol, produce salt and water retention and were even quite effective oral contraceptives! The reason for most if not all of these changes in metabolism stems from the fact that these drugs modified the function of the liver and that this was brought about by an untoward effect on certain important liver enzymes and organelles, an effect attributed to the alkyl substitution in the 17 carbon position of the parent hormone testosterone. It should be pointed out that these orally active anabolic steroids proved to be far more toxic than testosterone itself. Indeed, even large doses of testosterone have little if any effect on liver function or on the metabolic functions listed above, with the exception of salt and water retention. My experience with anabolic steroids, given perhaps to 100 patients, who were closely supervised, taught me two lessons. The first was, that the patient, while taking the medication could feel quite well. Nevertheless, in many of these subjects, untoward metabolic changes could be demonstrated which made the continued administration of the compound unwise on medical grounds. It should

cause no surprise that a drug may bring about impaired glucose tolerance, elevated cholesterol levels and many other metabolic changes without producing clinical signs. Metabolic changes such as those I have just mentioned, may be symptomless for many years and only come to light when a clinical event, such as a coronary thrombosis, draws attention to them. Even then, the connection between the metabolic changesa nd the untoward clinical episode may remain in doubt. For example, five of my patients receiving anabolic steroids suffered a coronary thrombosis while the drugs were being administered, or shortly after they were discontinued. All had elevated serum chlosterol levels due to the drug. No proof, however, that the drug caused the disease, coronary thrombosis, could be given in such a small group. An *apparently* harmless drug, taken over a prolonged period, may be responsible for the later development of serious illness, but a causal relationship might then be difficult to prove.

The second lesson was the realisation that any modification to a steroid hormone made a careful study of that drug's metabolic and other effects essential in case the modification was responsible for undesirable functional changes.