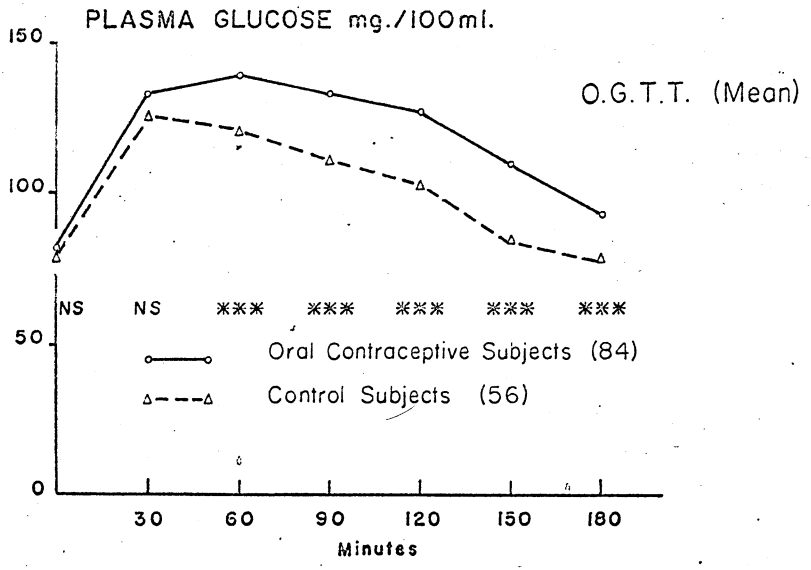

Fig. 1. Mean oral glucose tolerance test plasma glucose values in 56 control women and 84 of the test group.

With what may fairly be described as a high index of suspicion, I started to study the metabolic effects of oral contraceptives in 1964. In 1966, with my colleagues Dr. John Doar and Dr. Gervaise Mills, two papers were published in which we described some effects of oral contraceptives on carbohydrate (publication 71) and lipid metabolism (publication 72). Briefly, what we found was this. We studied two large groups of women—one group was using oral contraceptives (the test group) and the other group was not (the controls). The average ability of the test group to metabolise glucose during the course of a glucose tolerance test was significantly impaired compared to the control group. Fig. 1 shows the mean curves for both groups during the oral glucose tolerance test. About 18 per cent of the subjects in the test group had oral glucose tolerance curves which were abnormal as judged by generally accepted criteria. Only two per cent of the control group had such abnormal curves. This abnormality, which was mild in most cases, may be described as "chemical diabetes" to distinguish it from severer examples of the disorder which are found in symptomatic diabetes mellitus. Another abnormality which we found at this time was that the blood pyruvate levels were significantly elevated in the test group compared with the controls. For reasons which need not be expounded now, we considered that the glucose and pyruvate abnormality was most likely due to the oral contraceptive potentiating the metabolic effect of cortisol, the hormone, popularly called 'cortisone', produced in the body by the adrenal gland. As I shall mention later, further research supports this view. As the result of our early studies, therefore, we concluded that the oestrogen-progestagen contraceptives impair glucose tolerance and produce "chemical diabetes". Moreover the mechanism was probably to bring about a biological excess of cortisol, so that the disorder could be further categorized as "steroid diabetes".

The changes we found in the serum lipids (fats) were somewhat complex and need some prior expanlation. The fats circulating in the blood plasma or serum, when the subject has fasted for more than 12 hours, consist of cholesterol, triglycerides, and phospho-lipids. These three substances are associated together with a serum protein to form macro-molecular complexes referred to collectively as the lipoproteins. Various lipoproteins can be separated from the serum using a variety of physical or chemical methods. One method, employing the principle of ultra centrifugation (high-speed centrifuging) can be used to separate the lipoproteins into three classes referred to as high density (H.D.), low density (L.D.L.) and very-low density (V.L.D.L.) classes. The relative proportions of protein, cholesterol, triglyceride and phospholipid varies in each of these three classes of lipoproteins. With this preamble, I can now return to our serum lipid results. We found that the average serum cholesterol in the users was somewhat higher than in the controls, although not significantly so, while the serum triglyceride levels were much higher in the test group compared to the controls. Fig. 2 displays this effect.

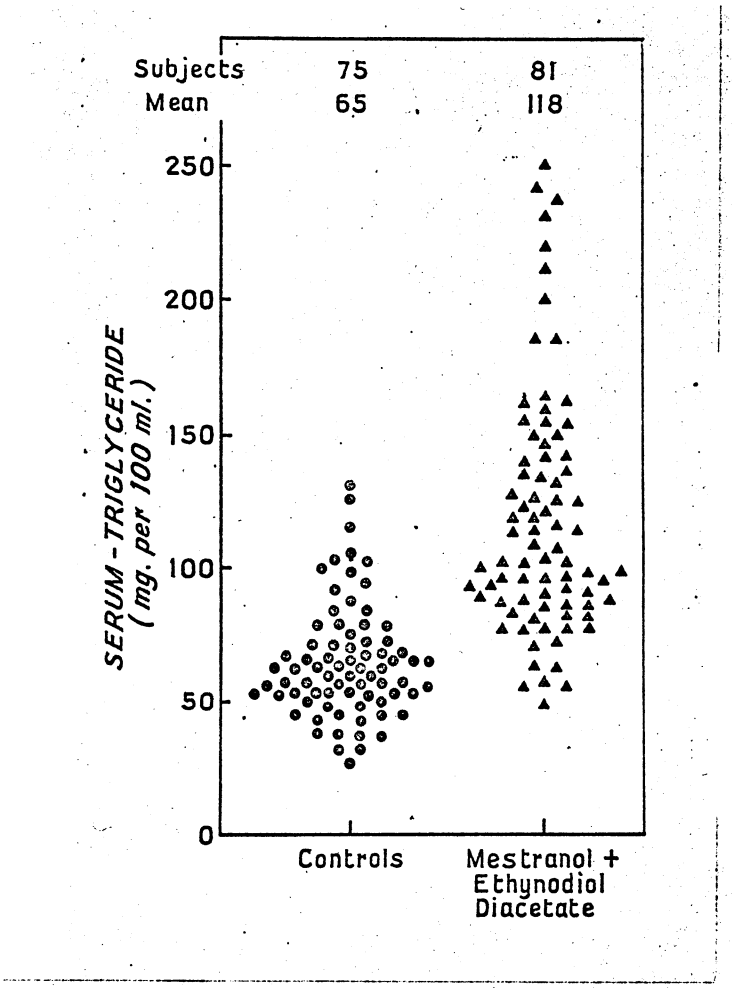

Fig. 2. Serum triglyceride levels in control and test groups receiving Ovulen.

In 30 per cent of the test group, the serum triglyceride values were above the highest value (131 mg/100 ml) found in the control group. The lipoprotein analysis using the analytical ultra centrifuge method showed that the low density and very low density lipoproteins were higher in the test group compared to the controls. These changes in serum lipid and lipoprotein levels seen in young women taking oral contraceptives caused their lipid values to resemble more the pattern found in men and post-menopausal women.

These two studies were disquieting because they showed the occurrence of two major metabolic abnormalities (impaired carbohydrate metabolism and elevated serum lipid levels) in a considerable proportion of women using oral contraceptive steroids. As I shall explain later, such abnormalities have been identified as "risk factors" in the accelerated development of occlusive vascular disease (atherosclerosis)—diseases such as coronary thrombosis, strokes, and other circulatory disorders. The possibility of oral contraceptives increasing the incidence of diabetes mellitus had also to be considered.

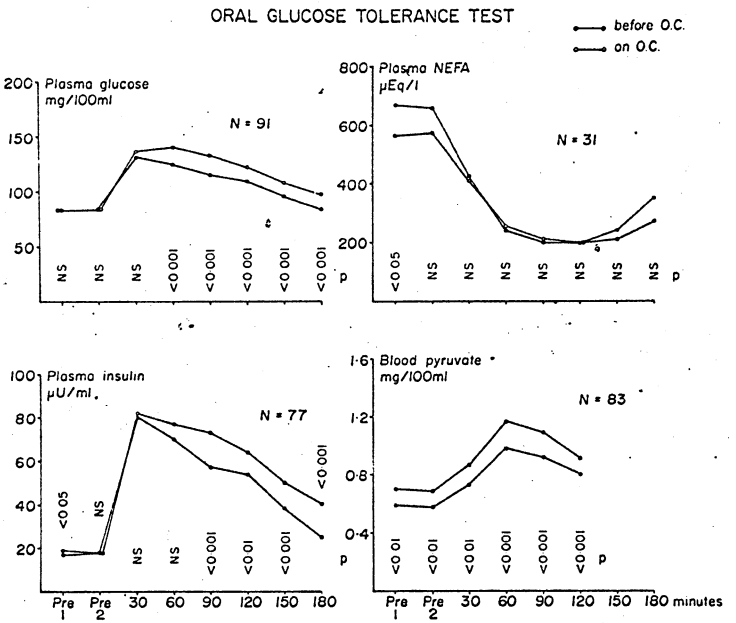

Fig. 3. Oral glucose tolerance test mean plasma glucose, NEFA, insulin and blood pyruvate levels in women before and during oral contraceptive administration.

N = number of women
NS = not significant

The studies I have referred to suffered from the disadvantage that to some extent the results depended upon the successful matching of control and test subjects, for such aspects as age, parity, degree of obesity and family history of diabetes, all of which may effect both carbohydrate metabolism and serum lipid levels. Therefore, in 1967, we set out to repeat the studies using the same women as their own controls. In addition, this enabled us to determine the proportion of women whose metabolism was affected when they took oral contraceptive steroids. We published our results in 1969 (Publication Nos. 75, 76, 77, 78, 79) and 1970 (Publication Nos. 80, 81 and 82). In these publications we have confirmed that glucose tolerance is impaired by oral contraceptive steroids and that in as many as 78 per cent of a group of 91 women, some deterioration of glucose tolerance could be demonstrated. In this group, 13 per cent of the women developed chemical diabetes during therapy. We also showed that plasma insulin levels were higher during the course of glucose tolerance tests when the patient was receiving medication compared with the control values. We confirmed the elevated blood pyruvate levels in oral contraceptive users. These results are shown in Figure 3 and given in full in Publication 79. To our previous data, we had now added another metabolic abnormality due to oral contraceptive medication, namely hyperinsulinism. I do not wish to dwell upon these abnormalities but will refer briefly to three further aspects which we have explored. We have shown that glucose tolerance usually returns towards normal six weeks to three months after oral contraceptive drugs are withdrawn (Fig. 4). We have also shown that in addition to enhancement of insulin secretion, hyperinsulinism, the reverse effect may be found in some patients and insulin secretion may be lower as the result of taking the medication. This abnormality is characteristically seen in sub-clinical diabetes mellitus.

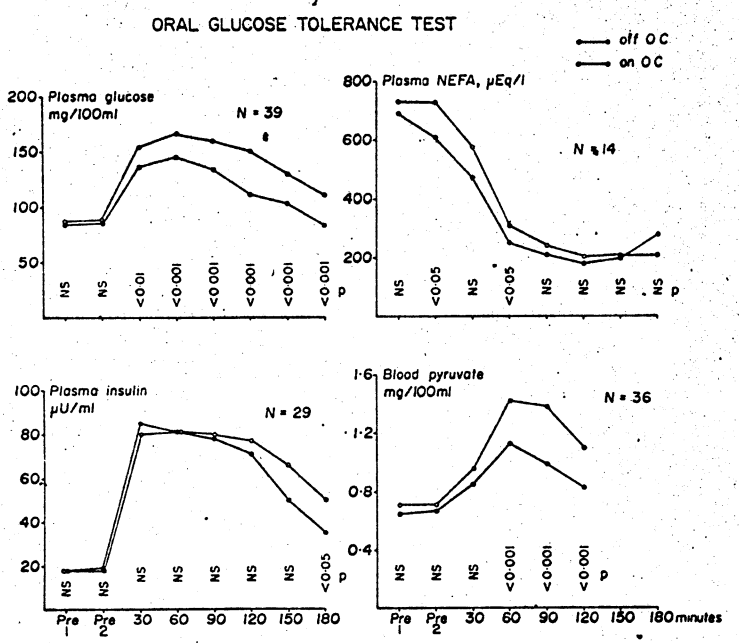

Fig. 4. Oral glucose tolerance test mean plasma glucose, NEFA, insulin and blood pyruvate levels in women during oral contraceptive administration and 6 to 12 weeks after stoping the drug.

Our study of lipid metabolism in oral contraceptive users also confirmed our original observations (Publications 78, 81). We found that in 164 subjects, serum cholesterol was slightly but significantly elevated, while they were taking oral contraceptives and serum triglyceride markedly so. About 90 per cent of the subjects showed elevation of serum triglyceride levels (Fig. 5). We also confirmed that the low density and very low density serum lipoproteins were higher when the women were using oral contraceptives, compared to the levels when they were not.

Neither in our studies of carbohydrate or lipid metabolism were we able to identify any patient characteristic such as age or family history of diabetes, which enabled us to predict in which patients these metabolic changes were likely to be most distinct, nor were we able to show any significant difference between the effect of various oral contraceptive combinations.

The methabolic changes I have outlined here have been confirmed in many studies and have been reviewed in detail in the Second Report on the Oral Contraceptives by the Advisory Committee on Obstetrics and Gynecology, Food and Drug Administration, August 1, 1969.

I would like now to describe very briefly five clinical cases which exemplify the metabolic changes I have described as being due to oral contraceptive steroids.

Case 1. E.M. (Fig. 6) is a young woman who exemplifies impairment of glucose tolerance (chemical diabetes) with high insulin levels due to contraceptive medication. She was without symptoms.

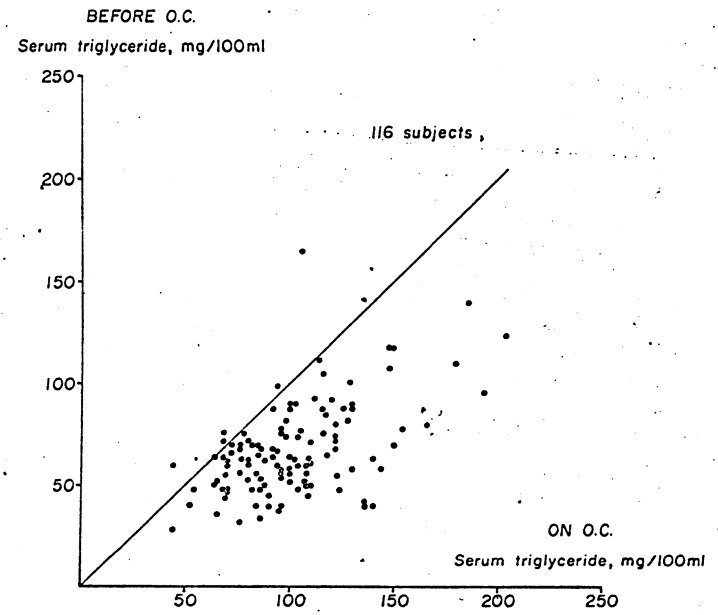

Fig. 5. Serum triglyceride levels on oral contraceptive therapy compared with the value in the same subjects before treatment.

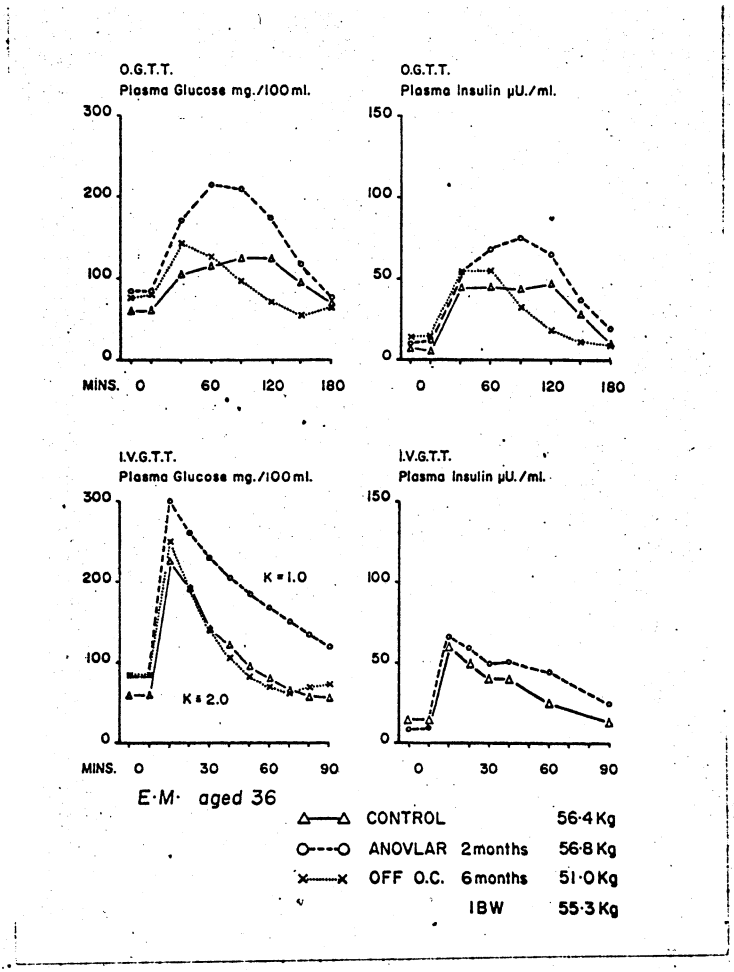

Fig. 6. Case 1. E.M. Oral and intravenous glucose tolerance and plasma insulin levels in a young woman when receiving and not receiving oral contraceptives.

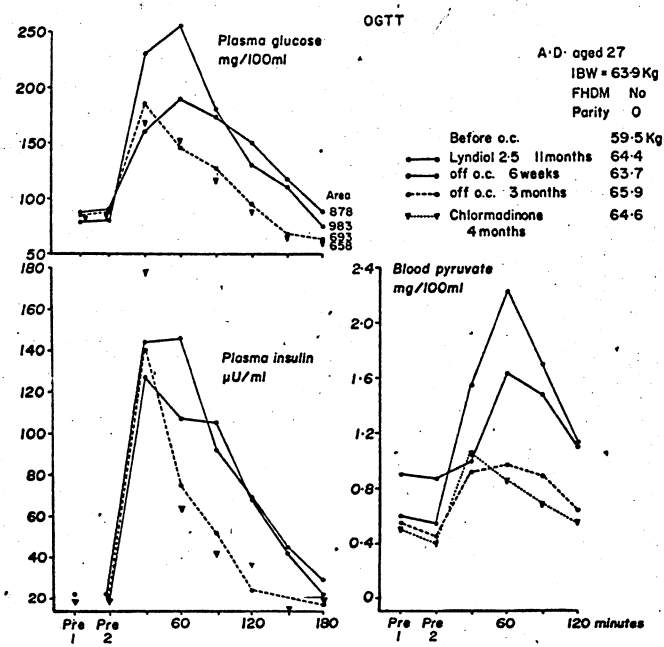

Fig. 7. Case 2. A.D. Oral glucose tolerance, blood pyruvate and plasma insulin levels in a young woman when receiving and not receiving oral contraceptive medication.

FHDM = family history of diabetes mellitus
IBW = ideal body weight
Chlormadinone = chlormadenone acetate 0.5 mg. a day.

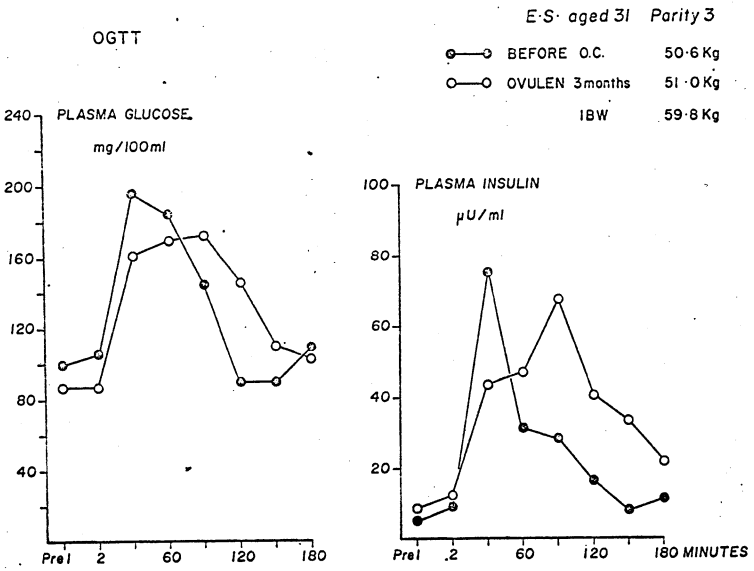

Fig. 8. Case 3, E.S. Oral glucose tolerance and plasma insulin levels in a young woman before receiving oral contraceptives and after three months of its administration.

IBW = ideal body weight.

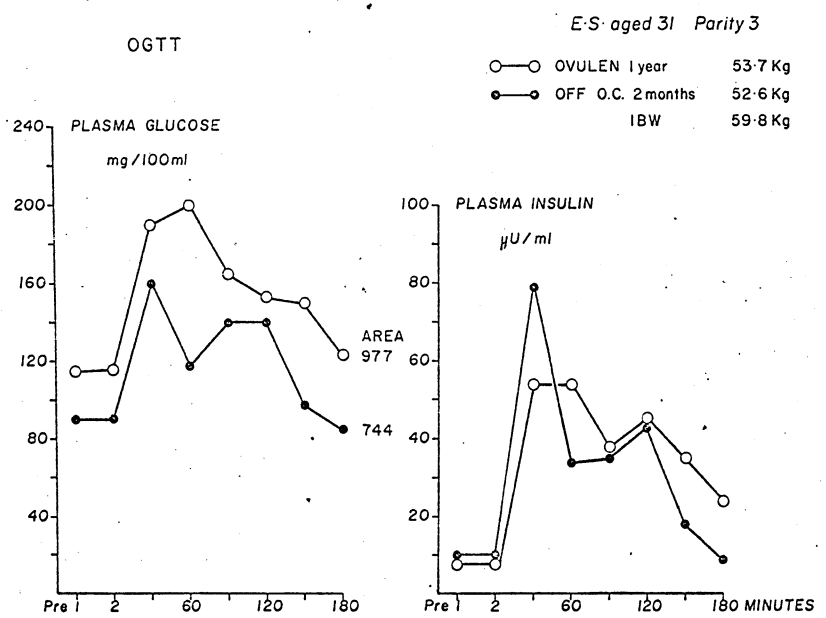

Fig. 9. Case 3, E.S. Oral glucose tolerance and plasma insulin levels in a young woman after one year on oral contraceptive administration, and two months after stopping.

IBW = ideal body weight.

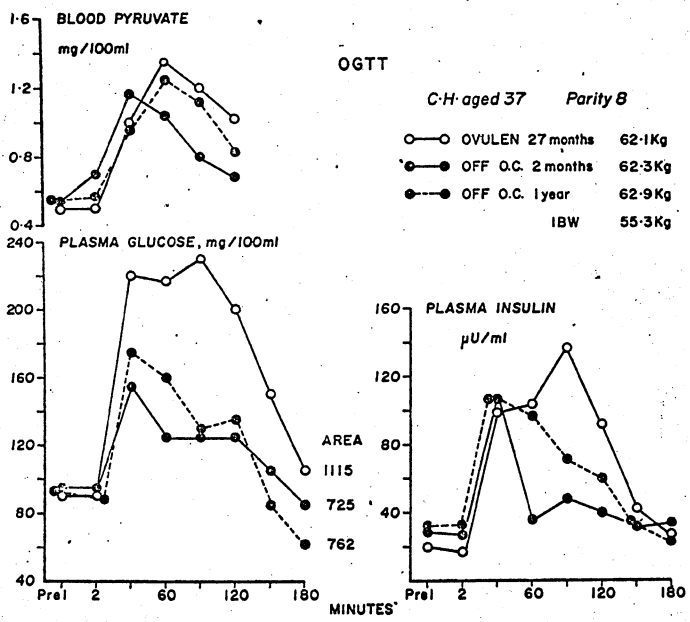

Figure 10. Case 4. C.H. Oral glucose tolerance, blood pyruvate and plasma insulin levels during and after oral contraceptive administration.

IBW = ideal body weight

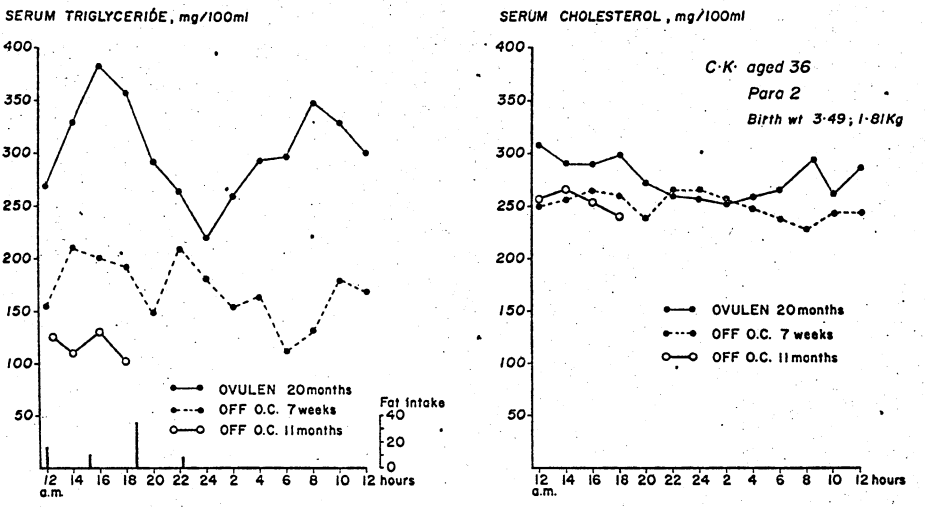

Fig. 11. Case 5, C.K. Serum cholesterol and triglyceride levels during and after the administration of oral contraceptives.
Blood was sampled at 2 hourly intervals throughout the 24-hour period.

Case 2. (Fig. 7) shows impaired glucose tolerance, high insulin levels and high blood pyruvate levels in a young woman taking oral contraceptives and the return of these variables to normal progressively over a period of three months, when the contraceptives were stopped. A low dose progestagen contraceptive (chlormadinone acetate) 0.5 mg a day administered for four months did not cause any notable change in carbohydrate metabolism. Again this woman was symptomless.

Case 3. E.S. (Figs. 8 and 9) shows glucose tolerance studies in a young woman tested before starting the medication, at three months, and 12 months of therapy, and three months after the drug's withdrawal. One can see the progressive development of true diabetes mellitus, with elevated fasting plasma glucose levels and abnormal glucose values in the glucose tolerance test combined with impaired and delayed insulin secretion. This abnormality was symptomless when it was discovered at 12 months and the metabolic abnormality disappeared when the drug was withdrawn. One wonders, however, what would have been the effect of the prolonged administration of this medication unhampered by any insight into what was happening to this patient's carbohydrate metabolism.

Case 4. (Fig. 10). C.H. shows the oral glucose tolerance of a patient who was referred because her blood pressure had become elevated after 27 months of oral contraceptive usage. The results show chemical diabetes and high insulin levels while on medication and the return of these variables to normal two months after its withdrawal. Her blood pressure (180 mm Hg systolic, 110 mm Hg diastolic) while on oral contraceptives also reverted to normal (120/70). Of further importance is that the patient was found by means of the electrocardiogram to have had a coronary occlusion, although this was symptomless.

Case 5. (Fig. 11) C.K. was referred because her blood pressure, previously normal, had become elevated after 20 months of treatment with oral contraceptives. The blood pressure was 150/110. This patient's oral glucose tolerance was abnormal. Her serum lipid values were strikingly abnormal. The triglyceride and cholesterol levels were measured in samples of bood taken every two hours throughout the 24 hour period. These values became normal several weeks after stopping the contraceptive steroid as did the blood pressure (120/80). Of special interest was the fact that this patient was shown also to have had symptomless pulmonary embolisation.

These studies have been selected out of many which could have been presented, in all of which the safety of the contraceptive medication is called into question.

I would like now to mention two other abnormalities which have been found in oral contraceptive users, because these must be understood before I can consider the possible influence of the metabolic changes on the health of the user. These two disorders are the abnormal clotting of blood and the development of high blood pressure (hypertension) in women taking oral contraceptive steroids.

Within a few years of the introduction of the oral contraceptive in Great Britain, sporadic cases of thrombosis involving both veins and arteries began to appear in the medical press. Several years, however, were to elapse before the first proof of an association between oral contraceptive use and the development of thrombotic disorders was established. In this respect, the work of Doctors W. H. W. Inman, M. P. Vessey and Richard Doll (British Medical Journal 27th. April 1968 p. 193 and p. 199) were outstanding. They clearly showed that there was a substantially increased risk of thrombosis occurring in veins, and in cerebral arteries, and a possible increase in coronary thrombosis in women using contraceptive steroids. Blood clots forming in the veins (thrombosis) can become dislodged and travel in the bloodstream, finally reaching the lungs to cause obstruction to the pulmonary arteries. This disorder is called thromboembolism. The risks of death from thromboembolism was increased about eight-fold in the user compared to the non-user of oral contraceptives. There was about a tenfold increase in the incidence of non-fatal thromboembolic attacks in the users which necessitated hospitalisation. The incidence of less serious forms of thrombosis was not reported upon. Fatal cerebral arterial thrombosis (stroke) showed a sixfold increase in incidence. There was almost a doubling in the incidence of coronary occlusion in women below the age of 45, but this did not quite reach the conventional level of statistical significance except in the youngest age group studied. In a similar type of study an American investigation essentially confirmed the British results, (Second Report on the Oral Contraceptive, Food and Drug Administration, August 1969, Appendix 2).

These reports on thrombosis stimulated a great deal of investigation into the mechanism of the untoward clotting tendency brought about by the oral contraceptive steroids. Many changes in various clotting factors have been found but there is little to be gained in enumerating them now since no certain description of the abnormality brought about by oral contraceptives can yet be given. I would like to draw attention, however, to an especially important abnormality induced by oral contraceptives. This concerns the abnormal behaviour of the small formed elements in the blood called the platelets. Abnormally in platelet function is thought by many to initiate the clotting process in arteries and probably in veins. An abnormal tendency of the platelets to stick to each other and to the lining of the vessel wall has been described in several clotting disorders including occlusive vascular disease and thromboembolism. This platelet abnormality occurs in women taking oral contraceptive steroids (see review by Doctors Marion Dugdale and A. T. Masi in Appendix 2D in the Second Report on the Oral Contraceptives).

Space does not permit me to deal at any greater length with the clotting abnormality, perhaps the most important single disorder which is so far known to be associated with the use of oral contraceptives. I must emphasize, however, that the incidence of serious clinical thrombotic episodes in women taking oral contraceptives is very low, only a few fatal cases occurring in 100,000 users every year. The non-fatal attacks, of course, are much more frequent, those requiring hospitalisation of the patient being about ten times commoner than the fatal attacks. But the *potential* significance of the abnormal clotting tendency is far greater than this, as will be mentioned later.

I shall refer briefly now to hypertension. This was first definitely identified with the use of oral contraceptives by Dr. J. H. Laragh of New York in 1967. A recent report by Dr. J. H. Luetscher (Annals of Internal Medicine, Vol. 71, November 1969, p. 891) gives a comprehensive account of the subject. Although this is an uncommon complication of oral contraceptive medication, these drugs caused, or substantially contributed to, the development of high blood pressure in about one third of the young women currently being referred to Dr. Luetscher's hypertension clinic.

With this cursory glance at two important problems, namely abnormal blood clotting and elevated blood pressure, induced by oral contraceptives, I now return to consider some implications of the carbohydrate and lipid abnormalities which I have previously described.

Atherosclerosis, popularly known as hardening of the arteries, is responsible for a great deal of mortality and morbidity (sickness) in human beings and accounts for the majority of deaths in many countries, including Great Britain and the U.S.A.

The incidence of the disorder varies within a country and from country to country and herein lies a great deal of its interest because it is obvious from the epidemiological study of the disease, that environmental (and hence probably modifiable) factors are very important in causing the disease, as well as hereditary and constitutional factors. The precise causes of atherosclerosis are not known. We do know that the accelerated development of the disease is associated with a number of factors and these are referred to as "risk factors". The disease is of earlier onset and of far greater prevalence in men below the age of 50 compared to women. Hypertension, obesity, heavy cigarette smoking and physical inactivity increase the risk. Diabetes mellitus is associated with a greatly increased risk and this is especially true in the case of women. Certain metabolic abnormalities are strongly associated with the disease and believed by many to be important risk factors. The best known is an elevated serum cholesterol level, but in more recent years, the importance of elevated triglyceride values has begun to be appreciated. I have previously referred to the serum lipoprotein pattern. Elevation in the low density and very low density lipoproteins, is thought to be an undesirable metabolic abnormality so far as atherosclerosis is concerned. Impairment of glucose tolerance, high insulin levels and, paradoxically, low insulin levels, are also thought to increase the risk of the accelerated development of atherosclerosis. Studies of insulin and triglyceride levels have only become possible on a large scale during the past few years and they have given us new insight into the problem of the development of atherosclerosis.

How important are these abnormalities of carbohydrate and lipid metabolism, and blood clotting in causing cornonary occlusion and stroke? Medical opinion is far from being uaninmous but the evidence implicating them in the disorder

as it occurs in relatively young age groups is overwhelming. The atherosclerotic lesion itself is not usually the cause of the final obstructive event. Most commonly, this is brought about by a clot forming in the blood and adhering to the vessel wall where it is damaged by the atherosclerotic process, thus obstructing the flow of blood through the vessel. It can be seen, therefore, that in many women taking oral contraceptive medication, the following potential risk factors may be operating, either singly or in combination, namely, abnormal glucose and insulin levels, abnormal serum lipid levels and abnormal blood clotting. Some have developed blood pressure as well. As far as we know, risk factors are additive in their effect. To give the Committee some indication of the importance attached to the metabolic (carbohydrate and lipid) abnormalities in the development of atherosclerosis, I have prepared a list of references (Appendix I) mainly from the literature published during the past three years. The list is by no means complete, and of course does not consider the clotting mechauism at all.

At this point, two important questions need to be examined. First, if these risks exist, why has occlsive vascular disease not become more of a problem than it is known to be be at the present time? The answer is that atherosclerosis, in most instances, is a very slowly developing disease and it may take ten, twenty or thirty years of exposure to the metabolic abnormalities ilsted above before clinical manifestations of the disease appear. Those women who have already developed venous orarterial occlusions while taking oral contraceptives have usually done so through the operation of the abnormal clotting factor which may have been the only identifiable cause of their illness. It is still far too early to expect the major clinical manifestations of atherosclerotic vascular disease to manifest themeslves as the result of oral contraceptive usage.

The second question is, are the metabolic abnormalities less important in the case of women than in man? I have already referred to the fact that in women before the menopause diseases such as coronary thrombosis are unusual compared to men. But this does not mean that young women possess a natural immunity which will protect them against the influence of untoward metabolic changes. Indeed, Dr. Michael Oliver, giving the G. A. Gibson lecture entitled "Ischaemic Heart Disease in the Young Adult" in October 1969 at the Edinburgh Royal College of Physicians, reported that in 135 women under the age of 45 with coronary artery disease the majority had abnormalities of lipid or carbohydrate metabolism. Whenever relatively young people with occulsive vascular disease are examined the incidence of abnormal carbohydrate and lipid metabolism is invariably high. One searching enquiry recently found such an association in 95% of the subjects tested ("Lipid and carbohydrate abnormalities in patients with angiographically documented coronary artery disease" by R. A. Heinle, R. I. Levy, D. S. Frederikson and R. Gorlin, American Journal of Cardiology, Volume 24, August 1969, p. 178).

I conclude, therefore, that the carbohydrate and lipid abnormalities produced by the oestrogen-progestagen oral contraceptive constitute an atherogenic risk. How many subjects will be affected and what period of exposure to the medication is needed to produce the disease are questions which cannot be answered at the present time. But the number at risk is large and the dangers inherent in the medication are therefore correspondingly great. This hazard is not one which can continue to be overlooked.

I should like to consider now very briefly the problem of diabetes mellitus in relation to oral contraceptive steroids. The clinical condition generally understood by the term "symptomatic diabetes" falls naturally into two categories although there is considerable overlap. An acute, usually severe disease is the type characteristically seen in young people below the age of 40. Insulin is required for its management in most cases. A more common form of the disease is that which occurs in older people and is called maturity-onset diabetes. Women are more affected than men, and these patients are often overweight and even frankly obese. This disease is usually insidious in its onset and may have existed for many years without causing symptoms until some precipitating factor such as an illness or surgical operation brings it to light. The disorder can often be treated by diet alone, or by oral hypoglycaemic drugs. Oral contraceptive steroids commonly exacerbate diabetes mellitus in both its forms when the condition is already established, or present in a latent but still symptomless stage. This is not surprising considering the fact that earlier I described the diabetogenic effect of the oestrogen-progestagen contraceptives. But whether or not these steroids can actually cause symptomatic diabetes (as opposed to symptomless

chemical diabetes) in a person not predisposed to the condition has not been established. As with atherosclerosis, maturity onset diabetes is a disease which evolves over many years. There are theoretical reasons for believing that oral contraceptives taken for several years could lead to irreversible changes in the pancreas and to symptomatic diabetes. An answer to this problem must, however, wait until further time has elapsed and the requisite clinical studies have been carried out.

So far in this statement, I have mentioned several important metabolic alterations caused by the oral contraceptives and have concentrated on those aspects which I consider likely to contribute to the development of atherosclerosis and diabetes. I have referred to the abnormal clotting disorders and to hypertension induced by these steroids. But there are many other metabolic changes which can be described in the users and the list continues to grow as investigators uncover more of the wide-ranging effects of this medication. These abnormalities contribute to many untoward symptoms encountered in oral contraceptive users such as weight gain and obesity, salt and water retention, liver dysfunction including jaundice, neuropsychiatric abnormalities such as anxiety, depression and loss of libido, chorea and increased susceptibility to attacks in epileptics, headache, migraine, weariness, changes in skin pigmentation, rheumatic complaints, leg cramps, vaginal moniliasis ("thrush") and an increased incidence of cervical erosion. I do not propose to discuss the biochemical abnormalities which underlie all of these untoward symptoms. Indeed, some of them have defied elucidation so far. These complaints, however, differ from the medical conditions with which I have been mainly concerned, since the remedy so far as the patient is concerned is quite simple. She merely stops the medication when the disadvantages due to the symptoms seem to outweigh the advantages of the medication. This, of course, is not the case in the woman in whom subtle metabolic changes are taking place which are producing no symptoms but could, in the end, result in serious ill health and even death. None of the alterations in the biochemistry of the body which I have enumerated are necessary for contraception but they are an inescapable consequence of the administration of synthetic oestrogen-progestagen ovulation inhibiting drugs.

At this point, we must question the desirability of using this method of controlling fertility. In a paper published in 1962 entitled "Suppression of Ovulation with Reference to Oral Contraceptives" in *Modern Trends in Endocrinology*, Butterworths, London, Dr. Gregory Pincus considered that in the application of ovulation suppression specifically for contraception three important criteria had to be met. The first was that the avoidance of any pathological side effect must be assured. The second was that the continuation of normal physiological function must be assured. Finally there should be no impairment of subsequent fertility by the medication. If these are the criteria by which the pill is to be judged, then I feel that the verdict must pronounce against the safety of the oral contraceptive. But the need for effective methods of contraception is great. I end, therefore, with a plea to those who have the authority, to ensure, by the provision of the necessary resources, and by their encouragement, that suitable alternatives to the steroidal contraceptives be found and made available in the shortest possible time.

ACKNOWLEDGMENTS

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Appendix I

Some recent references (mostly since 1967) to the association between abnormal carbohydrate metabolism, blood insulin levels, serum lipid levels and lipid metabolism and the development of occlusive vascular disease (atherosclerosis).

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Senator NELSON. What other studies have been made on metabolic effect related to the use of these oral contraceptives that are similar to yours, if any.

Dr. WYNN. There are, I should think, about half a dozen studies of both carbohydrates, that is to say the glucose abnormalities, and the lipid abnormalities, most of which were summarized in a book published in 1969 under the auspices of Harvard University entitled "Metabolic Effects of Oral Contraceptives and Steroids."

Senator NELSON. Were your studies published?

Dr. WYNN. They were.

Senator NELSON. Do the other studies confirm your data?

Dr. WYNN. In the opinion of the subcommittee responsible for "Second Report on the Oral Contraceptives" the answer to your question is "Yes."

Senator NELSON. Did you look at any of the other studies?

Dr. WYNN. Yes.

Senator NELSON. In your opinion were the results similar?

Dr. WYNN. Yes.

Senator NELSON. Have you read the package insert that is required to be included in the package that goes to the pharmacist or the physician?

Dr. WYNN. Yes.

Senator NELSON. From the standpoint of your studies in the field of metabolism, do the contraindications, warnings, and the indications cover the matters which you would feel ought to be covered?

Dr. WYNN. Well, the position, Mr. Chairman, is that late in December, I think on the 20th of December, I had a conversation with the Food and Drug Administration authorities, and they were good enough to ask me to comment on their package insert which they were then about to modify. Now I know they have modified it, but I have not had an opportunity to see the modified version, but I imagine that they will very substantially have covered the matters raised in my testimony, because they assured me that they intended to do so, and I believe I heard Dr. Hellman say this morning something somewhat similar, but if it is your wish I will try to obtain a copy of this insert and I will let you have it in writing tomorrow morning; my impression of it.

Senator NELSON. All right; I would like to have that whenever you get it with your comments which will be put in the record at the appropriate place.

Dr. WYNN. Certainly.

Senator NELSON. Thank you, Doctor.[1]

We have had a number of witnesses testify as to the importance of regular physical exams by those who are taking oral contraceptives. The time spectrum has varied from 2 or 3 months, which was the testimony yesterday of Dr. Laragh. So here is a professional in the cardiovascular field who thought blood pressure should be taken once every 3 months, and he adhered to that position when I raised a question as to whether 6 months was too long. Then we have had other testimony from Dr. Davis, who thought once every 6 months, with among other things a Pap smear and breast examination, and Dr. Kistner and Dr. Hellman all were within that period of 6 to 12 months, as I recall.

[1] This and other supplementary information, when available, will be incorporated in a subsequent volume.

Now, in terms of your studies and your concern about the importance of the metabolic changes, how frequently and what kind of examinations do you believe users of the oral contraceptives should have, and how often?

Dr. WYNN. Well, I think that this does pose considerable difficulties. As far as a physical examination is concerned, one has to be practical. There are economic factors and other social factors involved. I would think a physical examination every 6 months would be a minimum. If a woman is thoroughly examined every 6 months, that would be at least a reasonable minimum of clinical medical care.

Now, unfortunately, so far as the metabolic side is concerned, I personally think that nothing significant can be done or recommended. If you were to recommend that every woman have an oral glucose tolerance test with the measurement of serum lipid estimations every 6 months or every year, the cost of this medication would put it out of reach of everybody except those who are extremely wealthy. It is just not practical.

I might add that every time we carry out such an investigation on one of our patients, we are spending a considerable sum of money, some of it belonging originally to the American taxpayer.

So it is not practical to do metabolic investigations on a field sort of survey basis. It is only practical for these investigations to be carried out in specialized departments set up for the purpose, and I hope very much that far more of these departments will be set up in this country and in Great Britain than already exist.

But there should be a high index of suspicion. Certain patients should arouse the suspicion of the physician. A patient with a bad family history of diabetes, a patient with a bad personal history suggesting the possibility of subclinical diabetes, such as large babies or frequent unexplained abortion or malformation in the birth of the child, that sort of thing should arouse suspicion in the mind of the physician.

Now if a woman is given the oral contraceptive and gains weight rapidly, say 6 or 7 pounds in 3 or 4 weeks, and it continues to rise, that she has gained 10 or 14 pounds in a month or so, in my view that patient—either the necessary metabolic investigation should be carried out in her or the medication should be discontinued.

Another cause for suspicion that untoward metabolic changes are occurring would be the development of obvious water and salt retention, the swelling that women get in the hands and feet and around the face when they take the medication, if it persists, and if it is obvious, then those women—the reason for it is because of an untoward metabolic change, and either you investigate that patient or stop medication, depending upon the availability of facilities.

Senator NELSON. Thank you very much, Doctor.

Senator McIntyre?

Senator MCINTYRE. Dr. Wynn, the statement has been made here several times that the British findings regarding increased risk of thromboembolic disease with use of the pill cannot be applied directly to women in other countries including the United States. In fact, a statement to this effect was allowed in the official labeling of the oral contraceptives by FDA in 1968.

Moreover, the Sartwell study did come up with a different finding regarding the magnitude of the increased risk in the United States as opposed to Great Britain.

Do you know, Doctor, of any reasons why the British and the American female population should be any different with respect to the increased risk of thromboembolic disease resulting from use of oral contraceptives?

Dr. WYNN. Taking the women by and large, I think the answer to that question is no. I would not expect there would be substantial differences between British and American women so far as risk of thromboembolism is concerned.

What the data reveal is the very great difficulty of carrying out epidemiological studies. You see, you take the Sartwell study. It was not identical to the British study.

They identified over 2,500 cases—I am speaking from memory—2,500 cases of thromboembolism, but they excluded all but a small fraction, 176, for one reason or another. Now some of the reasons for exclusion were in my view unreasonable.

They excluded women with varicose veins and family histories of diabetes, and so on. Now in conversation with Dr. Sartwell, he has agreed with me that some of the reasons for exclusion were not really those which he would advocate at the present time. Be that as it may, it merely gives some indication of the great difficulties in this type of study.

You see, doctors sit around a table, and they ask themselves this question: Are women taking oral contraceptive medication at risk from thromboembolism? How do we know and how do we find out?

Well, the thing is to go into the hospital and find all the women who have had thromboembolism, and find out how many of them are taking the medication, but it is not as simple as that by a long means.

One has to take into account the spontaneous occurrence of the disease. One has to match the women that are found in the hospital with women who are not in the hospital, or if they are, are in there for some other condition.

All this poses tremendous and even profound epidemiological problems, and I do not think that we have the answer. I do not think that we have the solution to the epidemiological problem, and it is this which worries me more than anything else.

We can sit here and talk about the risks of atherosclerosis or hardening of the arteries. We can sit here and talk about the risks of the development of cancer.

We can sit here and talk about thromboembolism and its risks, and the risks of stroke, but the difficulties of proving with precision what is in fact happening are fantastic, and if I may just refer very briefly to the testimony of Dr. Goldzieher, he has taken out of Dr. Sartwell's study a table showing the great variability between the incidence of thromboembolism as it has been found in New York and Baltimore, compared to that found in another American city, and he says that this disproves the validity of the Sartwell study.

It does nothing of the sort. It is merely a statistical chance that those data came up the way they did, and all I can say is that is a very, very difficult problem. It must be left to the experts, and even when the

experts grapple with it, they can make a certain number of mistakes.

But if you are asking me is there any doubt about the association between thromboembolism and oral contraceptive medication, I want to answer quite clearly and unmistakably there is no doubt.

Now, sir, may I submit for the record a list of references to the association between thromboembolism and the use of estrogens in situations which have nothing to do with oral contraceptive medications. I have a list of 10 references since 1961, in which increased risk of thromboembolism has been described in men and in women, given estrogens for contraceptive purposes, including the suppression of lactation.

Senator NELSON. That will be printed in the record at this point.

(The document referred to follows:)

APPENDIX 2. REFERENCES TO INCREASED THROMBOEMBOLIC EVENTS IN PATIENTS TREATED WITH ESTROGENS OTHER THAN IN THE CONTEXT OF ORAL CONTRACEPTIVES

McDowell, F., Louis, S. and McDevitt, E. (1967) A clinical trial of premarin in cerebrovascular disease. J. Chron. Dis. 20, 679

Schrogie, J. J. and Solomon, H. M. (1967) Editorial—Estrogenic hormones and blood coagulation. J. Chron. Dis. 20, 675.

Veterans Administration Cooperative Urological Research Group (1967 Treatment and survival of patients with cancer of the prostate. Surgery, Gynecology & Obstetrics, 124, 1011.

Veterans Administration Cooperative Study of Atherosclerosis, Neurology Section (1966) An evaluation of estrogenic substances in the treatment of cerebral vascular disease. Circulation, Suppl. II, 33 & 34, 3.

Robinson, R. W., Higano, N. and Cohen, W. D. (1963) Long-term effects of high dosage oestrogen therapy in men with coronary heart disease. J. chron. Dis.. 16, 155.

Stamler, J. (1963) The relationship of sex and gonadal hormones to atherosclerosis. In (Atherosclerosis and Its Origins) Ed. Sandler, M. and Bourne, G. H., Academic, New York.

Lifshitz, K. and Kline, N. S. (1961) Use of estrogens in the treatment of psychosis associated with cerebral atherosclerosis, J. Am. med. Ass. 176, 501.

Oliver, M. F. and Boyd, G. S. (1961) Influence of reduction of serum lipids on prognosis of coronary heart disease. Lancet, 2, 499. (Ethinyl oestradiol—reduced cholesterol, but no effect on mortality from coronary disease—Dr. Somerville).

Daniel, D. G., Campbell, H. and Turnbull, A. C. (1967) Puerperal thromboembolism and suppression of lactation. Lancet, 2, 287–289.

Tindall, V. R. (1968) Factors influencing puerperal thromboembolism. J. Obstet. Gynaec. Brit. Comm., 75, 1324–1327.

Senator MCINTYRE. Dr. Wynn, finally, the statement you made about a soon to be published study relating oral contraceptives to coronary diseases is most disturbing. Are you at liberty, sir, to tell us anything more about this study?

Dr. WYNN. Sir, I hope, and I say I am addressing now the representatives of the world press who are sitting behind me, that they do not publish those remarks. Those remarks are for your benefit. The observations were sent to me and they will be published, but don't make a scare headline out of it.

Senator MCINTYRE. Would it be possible, Doctor——

Dr. WYNN. Do you want the details? I am prepared to reveal the details.

Senator NELSON. I would assume if it is to be published, in fairness to whoever is publishing it that the committee could wait.

Dr. WYNN. It will be published within 2 to 3 weeks. I was in contact with the individual yesterday on the telephone.

Senator NELSON. We will wait.[1]

Senator MCINTYRE. I think, Mr. Chairman, it might be well if some arrangement could be made so that a copy of this could be obtained and made a part of the record, the published study.

Thank you very much, Doctor.

Mr. GORDON. Dr. Wynn, on page 9 you state that "these changes in serum lipid"—is that the way you pronounce it, sir?

Dr. WYNN. You can pronounce it any way you like. It doesn't matter.

Mr. GORDON (continuing). "cause their lipid values to resemble more the pattern found in men and most-menopausal women." Are you saying here that young women who take the pill acquire certain characteristics of older people?

Dr. WYNN. In the respect of their serum protein patterns, yes.

Mr. GORDON. What is the significance of that?

Dr. WYNN. Well, the significance is that which I have described. The risk of the accelerated development of atherosclerosis.

Senator NELSON. That is a risk not yet proven?

Dr. WYNN. That is a risk which is not yet proven.

Mr. GORDON. One other question: I read some place that Dr. Howard Tifton of George Washington University is quoted as having said "liver function abnormality occurs in approximately 20 percent of women taking oral contraceptives." Do you have any comment on that?

Dr. WYNN. Well, Mr. Gordon, the term "liver function" as such is pretty well meaningless. It depends on what you mean and what you measure. The liver function abnormality means something to one doctor and something else to another.

Now, if you mean a conventional liver function test such as, for example, body rubin concentration in the blood level, which I imagine is what is meant, a conventional test, it doesn't surprise me that those changes have been found, although other people have reported lower incidence of abnormalities. More important than the conventional liver function test is to look at what is happening to the function of the liver as the seat, if you like, of many of the metabolic reactions which occur in the body, and here you find many abnormalities or alterations.

There is no doubt in my mind that many of the changes found in glucose metabolism and intermediate metabolism, which I haven't had a chance to go into, arise from alterations in the function of the liver, but that does not mean to say that the conventional liver function tests would reveal them.

If you will examine a liver with an electromicroscope, if you will take cells out of the liver and examine them under the electromicroscope of women taking oral contraceptive medication, you will find some extraordinary changes.

Mr. DUFFY. Dr. Wynn, Senator Dole regrets very much that he is required to make a quorum in the Agriculture Committee. He has several questions which he has left here, and which he would like me to ask you, and I will read them and perhaps for the sake of brevity

[1] This and other supplementary information, when available, will be incorporated in a subsequent volume.

in some instances you can answer generally, and then submit the balance of your answer for the record, if you don't mind and if the chairman does not object.

Senator NELSON. Are these questions Senator Dole's?

Mr. DUFFY. Yes, sir, they are.

The first question is what clinical data do you have which would suggest that these alterations in metabolism which you describe are in any way related to the inevitable production of damage, permanent or otherwise?

Dr. WYNN. Would you repeat your question, please?

Mr. DUFFY. What clinical data do you have which would suggest that these alterations in metabolism which you describe are in any way related to the inevitable production of damage, permanent or otherwise?

Dr. WYNN. Well, I have already described in this testimony two cases which raise a strong suspicion of damage to the health of the user.

Now we are seeing at the present time something like 800 women a year receiving oral contraceptive medication and we are investigating these women. The numbers therefore that you request change literally from week to week. I therefore would prefer at leisure to sit down and answer that question in detail with the most up-to-date figures that I have available.

All I can say is that I have seen, in terms of permanent damage, women developing coronary disease, stroke, pulmonary embolism, diabetes. These are the ones that I can think of quickly.

Certainly the commonest you may not consider significant, but I do from the point of view of the health of women, the very commonest abnormality, of course, is overweight and obesity.

This is quite common, and when I showed our data on this factor to certain visiting doctors who were themselves interested in the problem of oral contraceptive administration, they were amazed at how many cases I could show of really pathological obesity, that is to say an increase in body weight greater than 20 percent of the initial body weight of the patient.

Mr. DUFFY. Doctor, if there is something additional you would like to say on that, perhaps you would submit it for the record.

Dr. WYNN. Certainly.

Mr. DUFFY. Is there anything in the way you select your patients which might prejudice the development of these abnormalities you describe? Is it meant by this is there a history of overweight or a history of large babies, or perhaps abnormal glucose tolerances which might prejudice these results?

Dr. WYNN. It may be fatigue, but I am not understanding your question very well. Do I understand you to mean, are the data I am presenting biased in any way by nonofficial selection of patients? Is that the nature of your question?

Mr. DUFFY. I suppose that would be the thrust of it, yes, sir.

Dr. WYNN. In other words, if another investigator looking at the hundreds of patients we are investigating studied the same aspects, would they get the same information. Could we put it that way?

Mr. DUFFY. Well, supposing we say a different group of women. I think that would be the thrust of the question.

Dr. WYNN. Well, all women are women. Do you mean by a different group of women a group of women in another country, or do you mean economic status, grace? I am sorry, I want to be quite clear on the question.

Mr. DUFFY. Perhaps I should read this again. Is there anything in the way you select your patients that might prejudice the development of these abnormalities that you describe? In other words, is there a history of overweight?

Dr. WYNN. I have an idea of what you mean, a clearer idea of what you mean, and the answer is no. But I would like to refer you to our publications which I have submitted, in which we discuss subjects such as family history of diabetes, body weight, age. We have not looked at our data from the point of view of social-economic class or racial characteristics.

Mr. DUFFY. Doctor, the next question: Is it not correct that other investigators have found that many patients on the pill do not evidence these abnormalities you describe?

Dr. WYNN. Did you say many?

Mr. DUFFY. Many.

Dr. WYNN. A few investigators have found no abnormalities such as we have found. Some of the studies involve subjects as few as 15, taking the medication for a shorter period, as 10 days.

I have recently reviewed the data of all existing studies on metabolic effects, and this is covered in my publication No. 80, which is now in the press and will be available to the committee, but that precise question has been examined.

We look to see what some investigators published, data which did not seem to show much in the way of metabolic change, and when you excluded those studies which involve very small numbers and so on, the substantial opinion of all investigators is roughly the same, and this, as I say, was the conclusion reached by the subcommittee of the Food and Drug Administration.

Mr. DUFFY. The next question, Doctor, is during normal pregnancy certain hormones are present in elevated amounts but are biologically inactive. These hormones are also elevated by taking the pill. Are you sure that these hormones are not also biologically inactive?

Dr. WYNN. I can only say "Yes" to that, because you haven't specified which hormones are elevated during pregnancy or from taking the pill. If you want to go into it in greater detail, I shall be only too happy to do so.

Mr. DUFFY. There you have me at your advantage.

Dr. WYNN. I thought I might actually on that one. But to be quite fair, Mr. Duffy, I know very well what you mean.

Mr. DUFFY. You are most gracious.

Dr. WYNN. It is perfectly true that thyroid hormone is elevated. That is, the amount circulating in the plasma is elevated both in pregnancy and when people take the pill. It is perfectly true. And as far as we know, this does not mean anything much in relation to the biology of thyroid hormone excess. We don't have the exact answer to it, but we don't think it is very important.

Now in relation to the other hormone that you have in mind or your questioner had in mind, whoever he was, that is cortisol. Now, here I think our own data, which we presented in extenso, extensively, to the

National Institutes of Health on Tuesday of this week, our own data show that here you do have a biological excess of cortisol activity in pregnancy probably, though that is not the subject of our study, but certainly in oral contraceptive usage.

Mr. DUFFY. Doctor, the next question is how much of your data comes from higher dose pills? I suppose here we are talking about the earlier 5 to 10 milligram estrogen pill versus today's 1 to 2 milligram estrogen pill, and maybe you would also care to comment about this new minipill that they talk about.

Dr. WYNN. I would love to. The question of the dosage has been looked at very carefully by us, and we had not found substantial or statistically significant difference between the high estrogen pill and the so-called low estrogen pill, the difference being roughly 50 micrograms of estrodial in the low estrogen pill and 100 in the high estrogen pill.

In our own data we have not found any difference, but I do know of a very elegant study carried out in Great Britain, the data of which was shown to me just before I left, which suggests strongly that after 3 to 5 years of use, women taking the high dose estrogenic pill have substantially higher lipids, cholestrol triglyceride values, than those taking the lower estrogen dosage, and I reported this with the permission of the author to the NIH people on Tuesday.

Now, in relation with the so-called minipill, the minipill unlike the miniskirt is not here to stay, because last week or so the minipill was withdrawn by the manufacturers.

Senator NELSON. May I ask this question: Your statement that you did not find any difference between the 50 microgram and the 100 microgram pill, that applied to thromboembolism?

Dr. WYNN. No, that applied just to metabolic changes. The British Committee on the Safety of Drugs had come to the conclusion that the higher dose estrogen pills are more dangerous from the point of thromboembolism.

Senator NELSON. You are not disagreeing with the conclusion reached?

Dr. WYNN. Yes.

Mr. DUFFY. Thank you.

Senator NELSON. Thank you very much, Dr. Wynn, for your most thoughtful testimony. We appreciate your taking the time to come over here today, and your patience in the way you have testified.

Dr. WYNN. Thank you.

Senator NELSON. Our next witness is Dr. J. W. Goldzieher, director, Division of Clinical Sciences, Southwest Foundation for Research and Education, San Antonio, Tex.

Dr. Goldzieher, we appreciate your patience in waiting. We appreciate your being willing to take the time to come here today and give us the benefit of your well-known expertise in this field.

You may present your statement however you desire, and as with all the other witnesses, you may elaborate in places and summarize in places, whatever you desire. The statement will be printed in full in the record.

STATEMENT OF DR. JOSEPH W. GOLDZIEHER, DIRECTOR, DIVISION OF CLINICAL SCIENCES, SOUTHWEST FOUNDATION FOR RESEARCH AND EDUCATION, SAN ANTONIO, TEX.

Dr. GOLDZIEHER. Thank you, Senator Nelson and members of the committee. I appreciate the privilege of being here, and I am particularly happy to be here in the position of following Dr. Hellman. Dr. Hellman and I have served together on the World Health Organization Committee on Oral Contraceptives a couple of years ago, and I have followed with great care the deliberations and work of his advisory committee in his statement this morning.

In order to avoid repetition in going over a lot of material that he has already covered, I would like to——

Senator NELSON. May I interrupt. I neglected to say this. Some question was raised by somebody, whether you were a recommended witness or not. Let me say that Benjamin Gordon did an extensive job of consulting with a large number of people in making up a list of the best witnesses that we could find, and he compiled his list, and subsequently had a number of people making recommendations as to who ought to be on the list, and as I recall it, from four or five sources, everybody who was recommended was already on the list, save a few people who have yet to be invited. That will clarify the record. Your presence here is at our request.

Dr. GOLDZIEHER. Thank you very much.

On the basis of Dr. Hellman's previous testimony, and with your permission, I would like to skip over the initial page of my prepared statement, which tells about my qualifications in this field; I hope you will permit me to pass over this matter in the interests of time.[1]

I would like to address myself to several major points. The first one concerns the great variety of side effects which are attributed to the pill, and which are supposed to be passed on to women so that they can make informed decisions about whether they want to use the pill or not; and I would like to explore in a little more detail than has been done today, just exactly what we know about what we would call the minor side effects.

Then I would like to make some commentary on just two of the major side effects: (1) on how certain we are about the clotting phenomena, and (2) how certain we are about the cancer possibility; and there I might point out that——

Senator NELSON. I am sorry, did you have any biographical statement?

Dr. GOLDZIEHER. The first page. Would you care for me to read it?

Senator NELSON. That is fine. Where is it on the first page? Did you want to add anything to that?

Dr. GOLDZIEHER. Not particularly.

Senator NELSON. All right, I am sorry. I thought you might.

Dr. GOLDZIEHER. Let me address myself first to the question of whether we do or do not know how often women have adverse effects from the pill. In my opinion—and very surprisingly after these many years of research—I believe we do not, because the simple question of how often women have an adverse side effect turns out to be exceedingly complicated to answer.

[1] See information beginning at p. 6356.

As everyone knows, there are different ways of asking the same question, and depending on the way the question is asked, one gets different answers. Every Gallup poll or opinion survey recognizes the importance of this problem, which is a particularly difficult one in medical questioning. For example, it has been shown that if a leading question has been asked such as "have you have headaches—or nausea or depression—this month" rather than a question such as "how have you been feeling this past month," one will record a frequency of headache—or nausea or depression—which is four to six times higher than if the second, nonleading question is asked. One may say, why not use the leading question and get a maximum estimate? Simply because the use of this question will suggest to many individuals that they ought to be having this symptom even if they do not.

If it is asked repeatedly, as we do in our studies where we follow every patient every month, more and more subjects will think they ought to be having this particular effect, and will report accordingly.

Another problem is the great differences in population groups, which I believe is at least one factor which markedly differentiates the American experience from the British experience where the population is known to be much more homogenous.

I ask you to consider the results of one large clinical study we monitored, where the same drug, the same protocol and the same method of questioning were used in 18 different clinics—17 in this country and one in Mexico—and this study involved some 5,400 patients, and some 75,000 cycles.

If you will look at the diagram: in the first cycle of treatment the response to the nonleading question "how have you been feeling" produced frequencies of nausea which ranged from 0 all the way to 33 percent. Now the question is, which of these values is correct? And the answer is, all of them—and none of them. There is no single answer which tells the whole truth.

Consider also that each of these numbers assumes that each case of nausea—headache, depression, et cetera—was associated with the pill. Obviouly, women who do not take the pill also have nausea, depression, headache, et cetera from time to time. The real frequency is therefore some number less than the reported frequency. This spontaneous occurrence, the so-called placebo frequency, has been studied by very few groups aside from our own. There is a study in Switzerland, a study in Sweden, and there was one out at Stanford, and there is a double blind study in which we are involved at the present time.

One thing we did, before we got into the present double blind study, which is still simply an approximation to this problem, was to take our oral contraceptive questionnaire and simply apply those questions to a group of women who were coming into clinics for a routine checkup of their intrauterine device.

These women were not, and had never taken oral contraceptives; but the frequency of their complaints of headaches, depression, loss of sex drive and so forth were approximately the same as those of women who had been on the pill for 3 months or more.

A much better study—which appears in the book edited by Kipnis and others, and published earlier this year—is by Dr. Moos of Stanford. I have reproduced here some of his data where he asked women

premenstrually, intermenstrually, and menstrually, about mood swings, tension, and so forth, by a very careful protocol. It is an excellent study and probably the best one that has ever been done.

Interestingly enough, Dr. Moos came to the conclusion that women on the pill actually had fewer complaints than those who were not. Thus, a large percentage of the so-called side effects of the pill are probably not related to the pill at all, but are coincidental symptoms that women experience in the course of their everyday lives; only there is usually no one around to ask them about the way they feel, and to assume that everything they report is due to the pill.

There is a fourth——

Senator NELSON. I was going to ask a question. I notice that in that study, maybe he covers more, but covering the question of irritability in his study, the incidence of irritability is higher substantially for those who are not taking oral contraceptives; is this correct?

Excuse me, does it show the other? What does that chart show on irritability on page 3?

Dr. GOLDZIEHER. It shows that irritability is higher with no oral contraceptive.

Senator NELSON. Higher if they are not taking it?

Dr. GOLDZIEHER. That is right.

Senator NELSON. And lower if they are. It also shows the same for the title "Mood Swings" and the same for "Depression" and the same for "Tension." I am not qualified as a scientist, but I could imagine that the fear of pregnancy might cause all of those.

Dr. GOLDZIEHER. I certainly would agree with that.

Senator NELSON. If you become pregnant, you might have tension, depression, mood swings, and irritability.

Dr. GOLDZIEHER. And loss of libido, which I will come to in just a minute.

There is a fourth important factor which we all recognize but tend to forget when we try to associate pill-taking with complaints of various kinds. This is the psychological factor. In a very revealing study, a group of Swiss doctors kept women on the same type of contraceptive pill for several years, but every 6 months they changed the external appearance of the pills.

The next graph shows the results of that study. It shows clearly that every time the appearance of the pill was changed, a certain number of women began to complain of nausea all over again. Since there was no fundamental change in the medicine inself, this could only have been psychological.

The next figure shows the effect of changing the appearance of the pill on the women's sex drive. Obviously, sex drive is an extremely complex psychological phenomenon. Here this becomes evident. As women became accustomed to a particular pill, their sex drive improved, probably indicating, as you just mentioned, a release from fear of unwanted pregnancy. When the appearance of the pill was changed, they became anxious, since they could not be sure that the new pill was as effective as the old one. Their sex drive promptly diminished, since they were once again afraid of becoming pregnant. Over the next 6 months their assurance—and their sex drive—recovered. The Swiss doctors were able to repeat this pattern three times over. There can hardly be a better illustration of the importance of psycho-

logical effects, and of the difficulties of deciding whether a particular side effect is truly related to the chemicals in the pill, to other factors such as psychological influences, or to pure coincidence.

I should like to emphasize that I am not saying that side effects do not exist. I am saying that it is very difficult to distinguish pill-caused side effects from non-pill-caused side effects. Those who have very positive opinions about this either have double-blind studies that I am not familiar with, or perhaps do not recognize the difficulty of truly and objectively assessing this problem.

There are important side effects which occur rarely and which a knowledgeable physician would not ignore. In rare instances, the development of high blood pressure, of certain types of migraine headaches, of jaundice, is unquestionably attributable to a hypersensitivity of the individual to some or all of the components of a birth control pill. Hypersensitivity to drugs is nothing new Important adverse reactions occur with all drugs, as has been brought out in these hearings a number of times. There are fatalities from medicines as innocuous as smallpox vaccine. It is the responsibility of the prescribing physician to know these matters, and to sort out the danger signs from other information that the patient presents. This is part of the art and science of medicine. The patient is not well served by being asked to be his own diagnostician, by being given a list of possible complaints and dangers. Such information, which the ordinary untrained person cannot possibly use with insight and discrimination, serves only to confuse the situation, and make matters more difficult for the conscientious physician.

The next paragraph of my prepared statement deals with the question of metabolic effects. I should like to pass this by, for the simple reason that you have heard Dr. Laragh, you will hear Dr. Spellacy, and many other experts on the subject. I should like to make one comment, which is that the metabolic effects, most of which are quite similar to what is seen in pregnancy, have been described and known for a long time in that state. Thus they do not present anything fundamentally novel.

There are areas of agreement and areas of controversy. Where the certainty stops is exactly what has been pointed out today. The possible clinical inferences which can be drawn from these objective observations, and the point of assigning casual relationships is where scientists begin to disagree. Where I draw the line is, that if I take one supposition, add it on another supposition, then take on a third supposition—three probabilities which I do not know—and then conclude that I should take some positive action with respect to a particular patient, I am doing exactly what the scholasticists did 600 years ago when they argued about how many angels fit on the head of a pin.

I do not deny that it is a big disadvantage of the pill to have such widespread effects. An ideal contraceptive ought to have a single, highly selective action at some critical point in the reproductive process, and no other effects anywhere else in the body. All scientists recognize this point, and much work is being done to develop new classes of contraceptive agents which are more selective in their site of action.

I would not like to go in any depth into the problem of carcinogenisis. You have heard Dr. Hertz, with whom I have debated for

15 years in friendly fashion. He states his position; I state mine; and we agree to disagree.

You have also heard that there were two reports in the Hellman committee report. I would like simply to put a little perspective onto some of the statements which raise concern about the possibility of carcinogenisis.

In the first place, it is stated that there are five species of animals which develop cancers when given estrogens. It is not usually stated that other species, for example the guinea pig, do not.

It is not stated that certain inbred strains are also totally resistant, and that the positive experiments require a highly artificial animal exposed to fantastic doses of hormones for very long periods of time.

What this has to do with the hormonal exposure to which humans are exposed is a very dubious matter. At a meeting about 2 years ago, Dr. Gerald Mueller, professor of oncology at the University of Wisconsin, and one of the world's outstanding authorities on the relations of estrogens to cancer, was on a panel with me, and I purposely asked him this question, and I quote from his answer:

> Most of the tumors that have arisen in animals under these circumstances are dependent on the administered hormones to start with, and as soon as you take away the hormonal support, the tumors essentially evaporate from the scene. It is only after a long, progressive pushing of these tumors that some of them change to become hormonally independent. The data really argue for the fact that estrogens of their own accord are not primary carcinogens . . . To produce tumors in experimental animals, you usually end up using fantastic levels of hormones. I think the gross dosage used for experimental tumor production is completely different from what's used in contraceptive control.

It is also seldom mentioned in these expressions of concern that cancers have never been produced in the primate. I think this is terribly important, because thalidomide has shown us quite clearly that you can look in all sorts of animals and find nothing; and when you examine thalidomide in the primate, you get some answers. So I think it is terribly important, no matter how small the number of primates is, that cancer has never been produced by estrogen.

Furthermore, there are very interesting experiments, including one by Dr. Charles Huggins, a Nobel Prize winner, which showed that if you induce chemical cancers in mice, these chemically induced cancers can be suppressed or prevented by these female hormones which are supposed to be carcinogens.

On this basis, I thoroughly agree with Dr. Hertz, that we do not know the answer. The only place where we disagree is that he does not know and is unwilling to give any estimate of the probability of risk; and my feeling is, that since he has been saying the same thing for 15 or 20 years and has not come up with any new data, there is reason for some reassurance, even in view of the long incubation period of cancer, that nothing is going to turn up.

This table, which comes from an article in 1963, shows the number of cancers to be expected in a population of this size over this length of time, of women being treated with estrogens for menopause. The number of actual, observed cancers is recorded; this number of cancers, if anything, is less than would be expected if these women had taken no hormones at all, and had simply been observed over this period of time. Now, I am specifically not saying that this difference is a signifi-

cant difference. Iam saying only that in the available clinical information to date, there is nothing to support the claim that estrogens start cancer in women.

As a matter of fact, I might point out that a case can be made in the other direction. We know that certain women who have irregular hormone production because of ovarian disorders, and whose ovaries produce female hormones in an irregular fashion, and also produce male hormones and other abnormal hormones, are much more likely to develop pathological changes and possible malignancies of the uterine lining. Now, if it is a fact these abnormalities in hormone production are in some way related to these neoplastic changes, it would seem reasonable that the use of an oral contraceptive, which suppresses the abnormal ovarian hormones and produces an absolutely regular, exactly timed ebb and flow of female hormones, might actually be preventing the development of these neoplastic changes.

I want to emphasize that none of this evidence, either pro or con, carries sufficient weight to allow a final decision to be made. In this, I agree with Dr. Hellman and with Dr. Hertz.

The issue is far too important to be left to academic debate. It has been estimated that some 170,000 women—half on pills, half not—would have to be followed for a year to establish a two-fold rise in breast cancer, and about 120,000 women to establish a rise in cancer of the cervix. Such studies have been devised. Other experiments are being devised to test the problem of cancer of the cervix, and I am happy to say that we plan to cooperate with the FDA in utilizing our planned parenthood clinic to provide data for such a study.

One further point. The type of women who come to most of these planned parenthood or other birth-control clinics, have usually had an absolute minimum of medical care. As a matter of fact, all too often these women have never before had a routine pelvic examination and pap test. It is well known that a number of premalignant or early malignant changes are picked up by the routine pap screening of these women, and of the annual or semiannual pap screening, which is routine after the pill is started.

In the sense that improved screening is thereby made possible, this in itself will tend to lower the ultimate number of deaths from cervical cancer, and hopefully will steepen the drop which Dr. Hellman showed exists in the incidence of cervical cancer in this country.

Now I should like to address myself to the problem of thrombosis. I believe we have had unanimous agreement today that the British studies and the Sartwell epidemiological report conclusively prove a relationship between thromboembolic phenomena and the pill. I would like to suggest that to some scientists and to some statisticians the evidence is not quite so convincing.

There are many known causes for thromboembolic disease, the commonest being the birth of a baby. In fact, of all diagnosed cases of this disorder, at least 90 percent are associated with known predisposing factors. The big question is the other 5 to 10 percent for which no cause is apparent.

It has been repeatedly mentioned today that the frequency of this unknown thromboembolic disease, what we call idiopathic thromboembolic disease, has been rising rapidly since 1958 in both men and women; there is a chart here showing the rise in a London population, none of whom were oral contraceptive users.

I have no better guess than Dr. Hellman, as to why this should be so, but I suggest that since this is far more frequent and far greater a problem than anything that has been attributed by anyone to the pill, it merits at least as much attention as the pill does.

Now, how do we study this very difficult kind of a problem? One way is to study whether pill takers themselves have a higher frequency than other groups.

This was the test approach by Drs. Drill and Calhoun when they compared the rate of thrombophlebitis in pill takers in various clinics with the rates in certain other populations. I have reproduced here the data from their controversial paper. The frequency on their combination type contraceptive trials was 0.55 per thousand women per year, and it is compared for perspective to incidences in other types of populations. Now, this study has been very properly attacked. It was not intended to be a definitive study.

We recognize the fact that the population from which this figure was derived was from clinics where women were monitored all too seldom, and where the dropout rate in certain instances was very high. Therefore we decided to look at one of our collaborative clinical trials, where one single preparation was used and where every woman was checked every month by questioning as to whether she had any symptoms. This study amounted to some 360,000 cycles in approximately 10,000 women. Our value of 0.56 is incredibly close to the value of 0.55 in the Drill and Calhoun study, in spite of the fact that a different drug was used, a different method of questioning was used, a different computer analysis was used, and in spite of the fact that our women were looked at every month and theirs were not.

I can draw only one conclusion from this: that even increased monitoring of the population failed to show a dramatic change in the incidence of thrombophlebitis. At best, it says that a substantial risk in numbers does not exist. It does not constitute proof or disproof of the original contention.

Now, how do we answer the original contention?

There are two ways: (1) We can do a prospective study where 20,000 women who are going to go on contraception, some on pills, some not, are followed for 10 years, and we look for changes in the frequency pulmonary embolism and thromboembolic disease. This takes a long time; it is very difficult to find the populations and terribly expensive. As a substitute, and statisticians recognize that this is a substitute, the (2) retrospective approach has been used in England and in the Sartwell study in the United States.

The crux of the matter is the reliability of the retrospective study. You have only to look at Mainland's book, "Elementary Medical Statistics," and Berkson's numerous comments in the literature, or those of many other statisticians who emphasize the inherent risks of the retrospective study carrying within itself an unknown bias which changes the results.

Now, where would the bias come from? The bias comes from the fact that a retrospective study is only as good as the matching of the patients with the controls. In order to match a patient with a control, you should know every factor which could possibly influence that comparison, so that the only thing that is left unmatched is the pill-

no pill alternative. I submit to you, since most of the time we have no idea what causes idiopathic thromboembolic disease, it is not possible to carry out accurate matching.

As a matter of fact, the most important of the studies, the Vessey and Doll study—where they interviewed the patients, and went through the whole classical retrospective approach, and subjected their data to standard statistical tests—after they did all their matching, it turned out that the frequency of previous thromboembolic disease in one group was different from that of the other.

Now, the adviser to the Vessey-Doll study himself once said, in another statistical study, that if you find that an important factor is not adequately compensated in the matching process, then the whole study is invalidated; and I can give you that reference if you wish.

Therefore, I believe that what they did, which was to say, "Now, we will adjust our data and we will take only those sets that are now rematched" is not a valid, statistically acceptable way to study this problem; I submit that there are statisticians who would not accept the results of this study because it required post-data adjustment.

I don't wish to go into further statistical debates. I have discussed this particular study with Dr. Cochran of Harvard, Dr. Batson, and others, and they are all uneasy about the report.

What is more important is coming back to the question of bias. It turns out from a recent publication from the British literature that English women who take pills are heavier smokers than women who do not take pills; and smoking is a known contributory cause to thromboembolic disease.

Therefore, the question now arises, how much of the increased incidence of thromboembolic disease attributed to the pills is actually due to the fact that the pill takers in the British study were heavier smokers? I don't know the answer to that, but it does raise the question of how solidly one can accept the conclusion.

I want to make one further comment on the British study. Vessey and Doll, in print—and every other statistician will agree—clearly admit the fact that a study of this kind does not demonstrate a cause and effect relationship. It demonstrates only probabilities of association. Yet what has happened is, from the original statement that this does not establish a cause and effect relationship, we have crept by successive increments of not entirely convincing data to the point where we say this causal relationship is an established fact.

Now let us consider Sartwell's study, which has a considerably better design, but which, in the view of some statisticians, also has drawbacks. One of them, again, is the problem of the matching and the internal consistency. I show you here their own breakdown from their table 8, of the statistical risk of thrombophlebitis in different cities.

Senator McINTYRE. What page are you on?

Dr. GOLDZIEHER. Page 10.

Senator McINTYRE. I have it.

Dr. GOLDZIEHER. In their table 8, the data from Baltimore, Washington and Pittsburgh did not achieve statistical significance as far as an increased risk of thrombophlebitis was concerned. In New York, the difference of a factor of four was significant, and in Philadelphia a factor of 17 was highly significant.

Now, how are we to interpret these data? Are we to conclude that people who want to take pills should move from Philadelphia and New York to other cities?

Is there something mysterious about Philadelphia or New York that makes taking pills there more risky, or as is more likely and much more sensible, is this simply internal evidence that the sampling and the matching was not homogeneous from city-to-city? If this is true, we are again up against the eternal problem with the retrospective study: is the matching good enough that we can believe the conclusion?

I have said this simply to shake a little bit the absolute conviction with which the thrust of these studies has been put forth. I am not saying there is no risk. I am saying that the risk is not as well established or as certain, at least in my mind, as it is in the minds of some others.

Even if we accept the full numerical risk of the British and the American studies, this gets us to the question of is such a risk acceptable? What is an acceptable risk of death from a pill? There is no simple answer to this question.

There are those, of course, who say that noncontracepting women are healthy women and that no risk is acceptable. This is incorrect from the start, since even the World Health Organization's definition of health states "Health is a state of complete physical, mental, and social well being, and not merely the absence of disease."

Moreover, noncontracepting women are very much at risk—at risk of pregnancy, and pregnancy has associated with it a very real death rate. This death rate does not necessarily depend on obstetrical competence at all. It depends on social and economic status, on prenatal care, on nutrition or malnutrition, factors which are usually beyond the control of the obstetrician.

In our underprivileged groups, the death rate from the complications of delivery is five times as high as the 250 per million in our economically privileged groups, and if you go to a country like Ceylon it is not 1,250, it is 6,000–7,000 per million.

Thus, in 1 year in this country, of 1 million noncontracepting women, 800,000 will end up pregnant, and 200 to 1,000 of these women can be expected to die as a result of their pregnancy, depending on their socioeconomic status. Now, how can anyone say that there is no risk without the pill?

There are, of course, other methods of contraception which carry with them no risk of death from the method itself. With the rhythm method there is no method risk, but lots of pregnancies. It is estimated about 230,000 per million women per year. Of these 230,000 women, from 60 to 300, depending on economic status, will die as a result of their pregnancy.

The older mechanical devices (condoms, diaphragms) give better protection, but still 100,000 or more women will get pregnant of 1 million that use these methods for a year. There will be no method deaths, but the deaths due to these pregnancies will amount to between 30 and 300 per year.

Now, let us look at the newer methods. The table for this is on the next page. Of 1 million women using the intrauterine device for a year, about 50,000 can expect to get pregnant. There will only be about 12 to 60 deaths from the pregnancies, but as we have heard today, there are

deaths from the intrauterine device. The number is not known, but the rough estimate is of the same order of magnitude as deaths from oral contraceptive thromboembolic disease in America.

Thus, there may be 12 to 24 deaths per million users from the IUD itself, and these two factors add up to roughly 40 to 80 deaths per million women using the intrauterine device.

Now, we apply the same statistics to the oral contraceptives. We know that they are much more effective: There will be only about 10,000 pregnancies, and only about three to 15 of these will result in obstetrical death; then we have the claimed thromboembolic deaths of about12 to 24 per million, depending on whether you take the Sartwell or the British statistics. At all events, this adds up to 15 to 40 deaths per million women per year using the pill. On this basis, as far as I am concerned, it becomes clear when all the risks are considered, when all the methods are taken into perspective, that taking the pill is the safest thing a woman at risk of becoming pregnant can do in 1970.

These figures show only the bare bones of the problem. They do not take into account the fact that healthy women who become pregnant against their will often resort to criminal abortion. The sickness and death from this awful alternative cannot even be calculated. It has been estimated that one out of five to one out of 10 unwanted pregnancies is terminated by abortion.

On top of this, how can one measure, and how can one throw into the scales the anxiety, frigidity, maritial discord and infidelity that are generated by the fears of unwanted pregnancies and uncertain contraceptives? Perhaps such human values cannot be measured by computers and statistics, but the physician who has to face the patient day by day has to recognize this, has to put the problem into perspective.

I should like to turn to one other point. Given the uncertain information about side effects, given the probable but certainly not unequivocal information regarding thromboembolic deaths, given the serious question of metabolic disorders (which in my opinion at the moment must remain within the realm of scientific inquiry and supervision, and not in the realm of decisionmaking), given these circumstances—how can one give women a proper set of facts so that they can make an intelligent decision as to whether to use the pill or not?

Human beings are generally not impersonal decisionmaking machines. Emotions tend to color thinking, especially when life or safety is at stake. There are innumerable sayings, like, "The doctor who treats himself has a fool for a patient." How coolly and objectively can a lay person, a woman or her husband, weigh information and make a sensible decision, if they know that there is a risk of life or death, no matter how small, in the decision they make?

Aside from all emotion, making a sound decision requires having the necessary information and being able to evaluate this information correctly. It is certain that these hearings have produced one piece of information about which no one can quarrel: that even the experts on this subject disagree as to the interpretation of many of the available data. Literally centuries of experience have paraded before this committee, and there is no consensus. Is it then reasonable to suppose that a discussion between the physician and his patient, no matter how

careful and well intentioned will, in 10 or 20 minutes, so well orient that individual so that she can now make a truly informed decision for herself?

On occasion I have had patients who have discussed with me the various methods of contraception and then came back with PDR in their hand, and quizzed me about the side effects of the pill like a trial attorney. Such a patient needs, and deserves, every bit of cooperation and information the physician can give her, so that she can make a psychologically and intellectually acceptable decision.

But how many women like this do you suppose there are? Many women have heard that the pill is the most reliable of all contraceptives, and they want to be certain as possible that they do not get pregnant, and that is all they are interested in. Is the doctor serving her best by trotting out a long list of statistical uncertainties, and making her anxious about a course of action she is already content to take?

There are other women, on or off the pill, who have been frightened by misinformation and distortion of facts. They deserve to have all the information they can understand and utilize. Unfortunately, few physicians have the power of communication, as well as the exact information, to carry out this task as well as one would wish.

Finally, we must recognize that there are vast numbers of women who simply do not have inquiring minds like those that fill this room, and do not have enough education to comprehend much more than the simplest facts of biology. A misguided effort to "inform" such women leads only to anxiety on their part, and loss of confidence in their physician. They did not come for a lecture on statistics; they came for help in not having the 10th baby. The doctor is the man who is supposed to know such things, and they want him to tell them what to do, not to confuse them by asking them to make decisions beyond their comprehension. The sound physician, by judicious questioning, can determine which contraceptive method is most likely to be acceptable and effective in that particular woman. This is the prime consideration. Then it remains to be determined if there are any medical contraindications to that particular method, and we have discussed this at great length. But the idea of informing such a woman is not possible. It depends on the woman herself. It depends on her socioeconomic status. It depends on her education. It depends on her cultural pattern.

One final point I would like to address myself to, and that is the question of who should give the information to the inquiring woman? To make this point briefly: I feel, as a practicing physician, that it is my responsibility and all other physicians' responsibility. If a doctor wishes to use teaching aids in the form of pharmaceutical pamphlets, charts, sketches he makes on his prescription pad, so long as he gets the message across, this is the important thing. In no way can that responsibility be delegated to anyone else.

Finally, I want to comment on the package insert as a source of the information. I have been present at negotiations with the FDA, where the wording and the phraseology of these package inserts was worked on. I do not feel, as a scientist, that the wording of these inserts is intended basically and exclusively to inform the physician; it is in reality a compromise, an armed truce between the lawyers of the pharmaceutical companies who want to stay out of lawsuits, and the

FDA, who don't want to commit themselves to a statement which will get them in trouble; and, of course, always in the background is the pressure to make the product as interesting and promising as possible.

I don't think this makes for an article of communication which well serves the physician. I have been present when attorneys of a pharmaceutical company were willing to compromise on what I considered a fundamental medical point because they were afraid that, if they made too much of an issue, it could somehow hurt them in the pocketbook.

This is no way to make a useful package insert. I don't think a package insert which lists a grab bag of symptoms which have never been properly evaluated, and which have an uncertain correlation with the pill, serves to do anything except turn the doctor off, when he sees a long list which he knows can't be that bad because he just doesn't see it in his patients.

One of the most useful things that these hearings could do is to bring another orientation into the nature of the package insert or some other document, which is necessary to the physician who, I grant you, has not the time to read the 2,000 or so articles a year that are relevant to the problem of oral contraceptives. In the last analysis, wherever the doctor gets his information, it is his responsibility to share it with the patient, so that they jointly reach a sensible decision.

Thank you.

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

STATEMENT OF DR. J. W. GOLDZIEHER, DIRECTOR, DIVISION OF CLINICAL SCIENCES, SOUTHWEST FOUNDATION FOR RESEARCH AND EDUCATION

Before entering upon the subject of my testimony, I would like to establish briefly some of the qualifications of our research group, and to indicate why we believe we can speak with some degree of familiarity on the subject of adverse reactions and risks of the oral contraceptives. The Southwest Foundation for Research and Education of San Antonio, Texas, was one of the first 3 groups in the World to undertake studies of contraceptive pills; we got into this field at the invitation of Dr. Warren Nelson of the Population Council, which supported our efforts for a number of years. Since that time, our group, with much help of experts from many fields, has often led the way in establishing the technology for measuring side effects of these drugs. We have, over the years, pointed out the technical problems posed by such studies, and the care with which the answers must be interpreted. We have helped to design and monitor the largest collaborative trial of a particular oral contraceptive which has ever been carried out, and, with the help of Dr. Hines and Mr. King, we have developed an entirely new area of statistics—that of the mathematics of very rare clinical events—such as, for example, pregnancies with the Pill. On the basis of such work as this, Dr. Louis Hellman himself asked us recently to prepare an extensive discussion on the problems of clinical trials, to be published for the benefit of clinicians generally. This work has just appeared in the American Journal of Obstetrics and Gynecology. It represents the 62nd publication from our group on the subject of oral contraceptives since our first presentation in 1961. Finally, to indicate that our experience is not exclusively with abstract statistics or with clinic populations of underprivileged women, it should be recorded that Dr. Moses and I have been in private practice for many years, and therefore have continuing face-to-face contact with the problems of women who take the Pill.

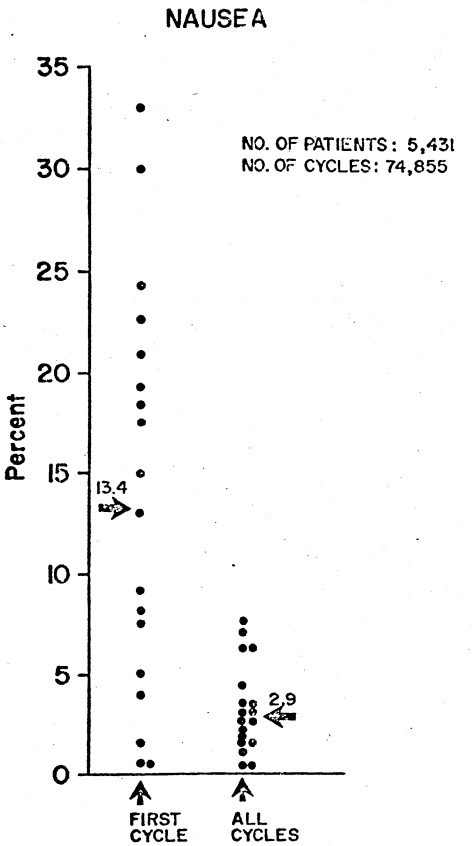
For the sake of simplicity, I should like to pose seven important questions regarding problems with the Pill, and attempt an answer to each.

Question 1. Do we know how often women have adverse effects from the Pill?

Answer: Surprisingly, we really do not. This seemingly simple question turns out, in real life, to be exceedingly complicated. As everyone knows, there are different ways of asking the same question, and depending on the way the question is asked, one gets different answers. Every Gallup Poll or other opinion

survey recognizes the importance of this problem, which is a particularly difficult one in medical questioning. For example, it has been shown that if a leading question is asked, such as "Have you had headaches (or nausea or depression) this month?" rather than a question such as "How have you been feeling this past month?", one will record a frequency of headache (or nausea or depression) which is four to six times higher than if the second, non-leading question is asked. One may say, why not use the leading question and get a maximum estimate? Simply because the use of this question will suggest to many individuals that they *ought* to be having this symptom even if they do not; if it is asked *repeatedly* during the clinical investigation, more and more subjects will think that they ought to be having it and will say so.

Another problem is that one gets different answers from different population groups. Consider the results of one large clinical study where the *same* drug and the *same* method of questioning were used in different clinics and hospitals throughout the country (Figure 1).



The frequency of reported nausea (which is a known, real side effect of the Pill) varied from almost zero to thirty-three percent! Which value is correct? All of them, and none of them. *There is no single answer that tells the whole truth.*

Consider also, that each of these numbers assumes that *every case* of nausea (headache, depression, etc.) was associated with the Pill. Obviously, women who do not take the Pill also have nausea, depression, headache, etc. from time to time. The real frequency is therefore some number *less* than the reported frequency. This spontaneous occurrence, the so-called *placebo frequency*, has been studied by very few groups aside from our own. We have published a study

where the questions usually asked of women taking the Pill were asked instead of women who came to a clinic for a checkup of their intrauterine device. These women were not taking contraceptive pills of any kind, but their complaints of headache, depression, loss of sex-drive etc. were about as frequent as those of women who had been on the Pill for 3 months or more.

R. H. Moos of Stanford feels that women on the Pill actually have fewer complaints than those who are not, as shown in this figure:

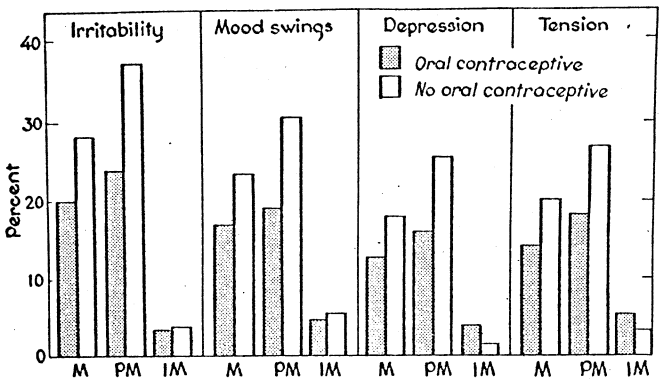


Fig. 7. Percent of women reporting moderate, strong or acute symptoms in oral contraceptives (O) and no oral contraceptive (NO) groups in menstrual (M), premenstrual (PM) and intermenstrual (IM) phases of most recent menstrual cycle - selected symptoms on negative affect scale.

Thus, a large percentage of the so-called side-effects of the Pill are probably not related to the Pill at all, but are *coincidental* symptoms that women experience in the course of their everyday lives—only there is usually no one around to ask them about the way they feel and assume that everything they report is due to the Pill.

There is a fourth important factor which we all recognize, but tend to forget when we try to associate pill-taking with complaints of various kinds. This is the psychological factor. In a very revealing study, a group of Swiss doctors kept women on the same type of contraceptive pill for several years, but every 6 months they changed the *external appearance* of the pills. The results are shown herewith.

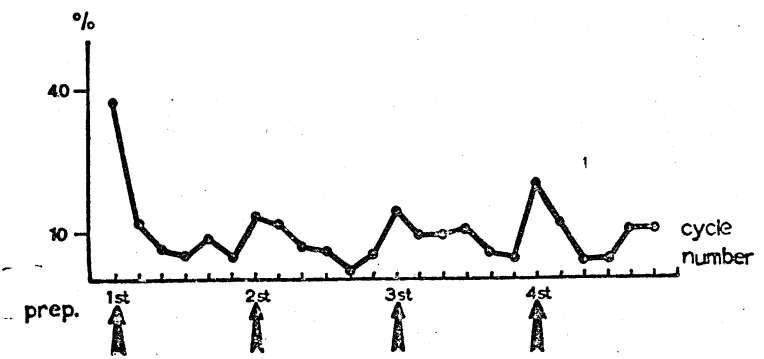


Fig. 3. **Frequency of nausea in 24 cycles (all combination preparations; centre No. 2).**

Richter et al., 1966.

The figure shows clearly that every time the appearance of the pill was changed a certain number of women began to complain of nausea all over again. Since there was no change in the medicine itself, this could only have been psychological. In the next figure, the effect of changing the appearance of the pill on the women's sex drive is shown.

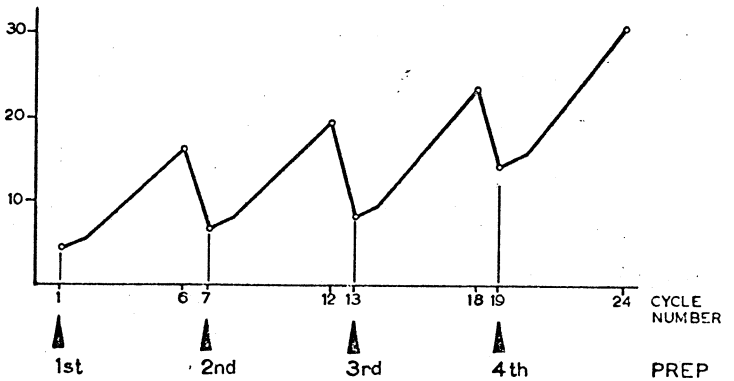


Fig. 5. Libido (all combination preparations; centre nr. 2)
——— increased.

Richter et al., 1966.

Obviously, sex drive is an extremely complex psychological phenomenon. Here this becomes evident. As women became accustomed to a particular pill, their sex drive improved, probably indicating a release from fear of unwanted pregnancy. When the appearance of the pill was changed they became anxious, since they could not be sure that the "new" pill was as effective as the "old" one. Their sex drive promptly diminished, since they were once again afraid of becoming pregnant. Over the next 6 months their assurance—and their sex drive—recovered. The Swiss doctors were able to repeat this pattern *three times* over. There can hardly be a better illustration of the importance of psychological effects, and of the difficulties of deciding whether a particular side-effect is truly related to the chemicals in the Pill, to other factors such as psychological influences, or to pure coincidence.

This is not to say that side-effects do not exist. It says, that to distinguish them from *other causes of the same symptoms* is very difficult, and that those who are dogmatic about these things are very likely to be biased to begin with, or are perhaps simply uninformed about the difficulties of getting meaningful answers.

There are important side effects which occur rarely and which a knowledgeable physician would not ignore. In rare instances, the development of high blood pressure, of certain types of migraine headaches, of jaundice, is unquestionably attributable to a hypersensitivity of the individual to some or all of the components of a birth-control pill. Hypersensitivity to drugs is nothing new. Important adverse reactions occur with all drugs, and there are fatalities from medicines as innocuous as smallpox vaccine. It is the responsibility of the prescribing physician to know these matters, and to sort out the danger signs from other information that the patient presents. This is part of the art and science of medicine. The patient is not well served by being asked to be his own diagnostician, by being given a list of possible complaints and dangers. Such information, which the ordinary untrained person cannot possibly use with insight and discrimination, serves only to confuse the situation, and make matters more difficult for the conscientious physician.

It is well known that all female hormones produce a variety of chemical (metabolic) changes throughout the body. You will hear experts like Drs. Laragh and Spellacy talk about some of them. Many changes have been described in a great variety of bodily systems, and undoubtedly, the more carefully we look, the more of them will be discovered. In essence, these changes are very similar to, but usually of a lesser degree than, those seen in normal pregnancy. In this sense, the changes that have been reported are not particularly unexpected. From the vast number of studies that have been carried out in pregnant women, we know that these changes disappear rapidly when the pregnancy terminates. In the use of the Pill, there is not an exposure to a continuous, high level of hormones for a period of nine months. There is about one week's rest in every four. Perhaps this is why the changes that are observed are seldom as marked as in pregnancy

itself. *At the present time we cannot state with any certainty the degree of risk or absence of risk associated with each measurable change.* It is some comfort, for example, to note that the changes in the blood clotting mechanism which occur normally *during* pregnancy are *not* associated with an increased tendency toward thrombosis or pulmonary embolism. On the other hand, we cannot simply ignore the existence of the many hormone-induced changes: they must be studied in depth and their contribution to any risks of pill usage must be assessed, and then balanced against the benefits of the Pill. In Appendix 1, I have tabulated a number of significant statements regarding indeterminacy or absence of risks as given by the experts included in the Salhanick book on "Metabolic Effects". Hopefully, they will help to improve the perspective on these questions.

Quite obviously, it is a big disadvantage of the Pill to have such widespread effects. An ideal contraceptive ought to have a single, highly selective action at some critical point in the reproductive process, and no other effects anywhere else in the body. All scientists recognize this point, and much work is being done to develop new classes of contraceptive agents which are more selective in their site of action.

Question 2. Do we know that there is an increased risk of cancer from taking the Pill?

Answer: We do not. In fact, the whole question of hormones as a causative of human cancer is highly controversial at present.

Interest in the relationship of hormones to cancer dates back at least 35 years, to experiments performed by a Frenchman on some highly inbred strains of *male* mice given huge doses of estrogen (female hormone) for long periods of time. Since then, all sorts of tumors have been produced in about 5 species of laboratory animals by hormone treatments. However, it is highly questionable whether these experiments have any relationship to cancer in humans. Usually, special strains of animals must be used for these studies, because some strains are totally resistant to developing tumors from hormone treatment. Relatively huge doses of these hormones are given to the animals for very long periods of time; such drug exposure bears no relationship to anything humans might experience.

At a recent scientific meeting, Dr. Gerald Mueller, Professor of Oncology (Cancer) at the University of Wisconsin, and one of the world's outstanding authorities on the relation of estrogens to cancer, said the following about the tumor experiments in animals: "Most of the tumors that have arisen (in animals) under these circumstances are dependent on the (administered) hormones to start with, and as soon as you take away the hormonal support, the tumors essentially evaporate from the scene. It is only after a long, progressive pushing of these tumors that some of them change to become hormonally independent. *The data really argue for the fact that estrogens of their own accord are not primary carcinogens* * * * To produce tumors in experimental animals, you usually end up using fantastic levels (of hormones). I think the gross dosage used for experimental tumor production is completely different from what's used in contraceptive control." Nevertheless, there are scientists like Dr. Roy Hertz, whose almost ritual expressions of alarm have changed little over the past 20 years in spite of accumulating evidence to the contrary. He talks about the various species of animals that can get experimental tumors, but he does not mention some, like the guinea pig, that are totally resistant. He does not mention that the tumors nearly always disappear when the hormone is withdrawn. He never mentions the experiments of Nobel-Prize-winning Dr. Charles Huggins, who showed that chemically-induced breast tumors in mice can actually be *suppressed or prevented* by injection of the supposedly dangerous female hormones. He never emphasizes the fact that no experiment to date has been able to produce a hormone-induced cancer in monkeys, the species most closely related to man.

An argument has been made of the fact that it takes a long time for cancers to develop, and we cannot therefore say anything about the dangers of tumor production by the Pill at this time. It is estimated that this time-lag is of the order of ten years, although this is not much more than an educated guess. It is true that the Pill has only been used about 13 years, and that really large numbers of women did not start to use it until about 5–6 years ago. However, estrogens have been around for thirty-five years, and have been taken for the treatment of menopause and other disorders by millions of women. We should therefore expect to see by now some evidence of the harmful effect of these hormones.

if it exists. The available evidence fails to show it, as seen in the following table, where the *expected* number of tumors and the actual, *observed* number of tumors in women taking female hormones for long periods of time are compared.

CUMULATED EVIDENCE ATTESTS TO SAFETY OF ESTROGEN THERAPY†

†Adapted from Bakke, J. L. West. J. Surg. 71:241 (Nov.-Dec.) 1963.

	PT.-YRS.	NO. PTS.	DURATION (YRS.)	EXPECTED CANCERS	ACTUAL CANCERS
Gordan[1,2]	1,200	120	14	12-15	0
Wilson[3,4]	2,604	304	17	20	0
Wallach[5]	1,480	292	25	22*	5**
Schleyer-Saunders[6]	.....	500	15	30*	0
Geist[7]	.....	206	5.5	12*	
TOTALS		1,422		96	5**

*Investigator's estimate.
**Uterine cancers—only one of these occurred after 1945.

There are, if anything, *less* tumors occurring in women on hormones than in those taking no hormone at all. Dr. Hertz's objection to these figures is that they refer to older women, and that a younger age group is on the pill. The implication is that the two age groups are somehow different in their susceptibility—an assumption for which proof is lacking.

If there is any connection at all between female hormones and the occurrence of cancer in women, it seems to appear when there have been long-standing disturbances of the regular monthly ups and downs of the female hormone levels. Since the Pill produces an absolutely regular, exactly-timed ebb and flow of these hormones, such disturbances, if they exist, are automatically corrected by the Pill. It may be argued that in such women, the hormones of the Pill actually *lessen* the risks of spontaneous tumor development.

None of this evidence, either pro or con, carries sufficient weight to allow a final decision to be made. The issue is far too important to be left to academic debate. It has been estimated that some 170,000 women (half on Pills, half not) would have to be followed for a year to establish a twofold rise in breast cancer, and about 120,000 women to establish a rise in cancer of the cervix. Although such an undertaking is staggering in its size, costs, and difficulty, it is absolutely essential that it be done, and current effort to carry out such studies deserve the fullest support.

There has been considerable publicity with regard to the possibility of cancer of the cervix being caused by the Pill. The latest controversy was generated by a report emanating from New York City. This work was of such poor scientific quality that it was rejected out of hand by scientific editorial review in this country, and it finally managed to get itself published in an English journal, one of several noted for their lack of editorial discrimination. The authors themselves admitted flatly that their findings *did not establish any cancer-producing influence of the Pill.* In particular, the study failed to show any increase in cervical cancer with continued use of the Pill, which would be expceted if there was a causal relationship. This negative finding simply echoes what others have been observing in their clinics for years.

It is standard procedure among physicians and in clinics to perform a screening test for cervical cancer (the "Pap" test) before the Pill is prescribed, and annually thereafter. In this way numbers of undetected cervical cancers are picked up. It has been shown that such detection programs eventually decrease

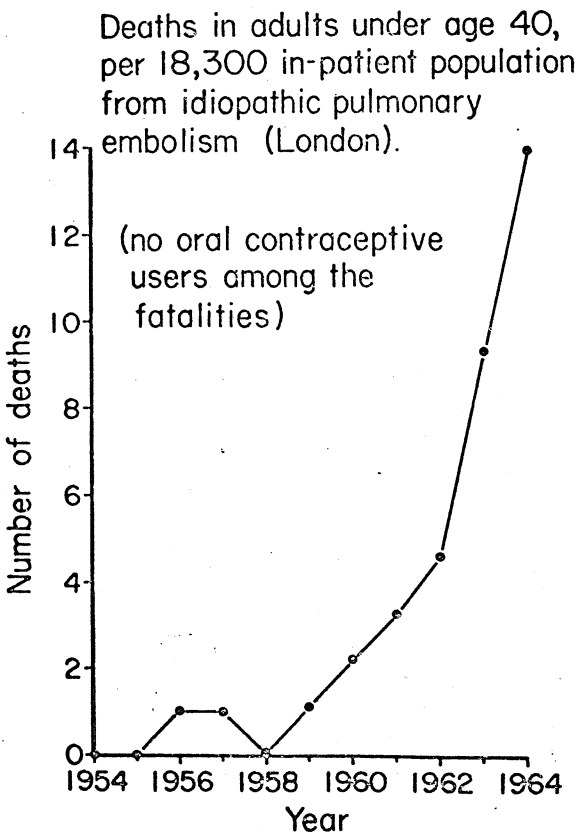
the number of deaths from cervical cancer. Since it improves cancer screening, use of the Pill will actually lower the ultimate number of cases of cervical cancer: in other words, the Pill serves, in a certain sense, as a cancer preventive.

We see, therefore, that the problem of cancer and the Pill has two sides. On the one hand, there is enough scientific information to concern researchers and necessitate much further work. On the other hand, there are both theoretical and practical reasons why the Pill may actually be a cancer preventive. It hardly seems reasonable that women should avoid the Pill and run the risks of far less effective methods, while this esoteric debate is going on.

Question 3. Do we know for certain that the Pill increases the risk of death from thrombosis?

Answer: At the present time, we do not.

Blood clots in the veins and chunks of clot breaking off and lodging in the lungs (pulmonary embolus) are much more common in young people than was believed just a few years ago. There are many known causes for this disorder, one of the commonest being the birth of a baby. In fact, of all diagnosed cases of thromboembolic disease, at least 90% are associated with known predisposing factors. The big question is the other 5–10% for which no cause is apparent. The frequency of thrombosis of unknown cause has been rising rapidly since 1958 in both *men* and women:



In a British study of deaths in young adults, this dramatic rise is shown. The rise began long before the use of pills was widespread. Nevertheless, it is important to note that there was not a single Pill-user among these fatalities. In

the face of this spontaneous, rapid rise in the frequency of embolism, it becomes most difficult to find out whether there is any *additional* increase in embolism as a consequence of the use of the Pill.

One way to study the problem is to see whether the pill-takers show a higher frequency of such troubles than other groups. This was the approach taken by Drs. Drill and Calhoun when they compared the rate of thrombophlebitis in pill-takers with the rates in certain other populations. Their value of 0.55 cases per thousand women per year was no different from the rates of several other comparison not taking the Pill:

Incidence of thrombophlebitis in nonpregnant women of childbearing age

Based on:	*Annual rate (per 1,000 women)*
Hospital admissions (U.S. and Canada)	0.91
Visits to physicians (England)	1.3–2.6
Visits to physicians (U.S.A.)	1.2–3.0
Antenatal incidence	0.74
Combination contraceptive trials (50,781 w/y)	0.55±0.37
Monthly-check sequential trials (27,959 w/y)	0.56

These statistics were attacked on the ground that follow-up of the Pilltakers was not adequate and that cases of thrombophlebitis might have gone unreported. We therefore undertook a similar study in a collaborative trial we have been monitoring, where patients were questioned *every single month* as to their health. In an aggregate of over 360,000 months of experience in about 10,000 women, we came out with an answer of 0.56 cases per 1,000 women per year, in startling agreement with the figure of Drill and Calhoun. Evidently, even a much more careful followup and a low dropout rate failed to turn up significant numbers of unreported cases. However, we are the first to admit that such data are, *at best, only indicative that a substantial risk does not exist.* They do not constitute proof or disproof of the original question.

The best way known to obtain answers to such difficult problems is to carry out what is called a prospective study. Such a study, for example, would observe 20,000 women started on the Pill and 20,000 women started on some other type of contraception for 5–10 years, and see if there is eventually a difference in the frequency of clots. This is obviously a monumental and costly undertaking. A quicker and cheaper way to try and arrive at an answer is to take a backward look instead of a forward look. This is called a retrospective study. It hinges on the matching of patients with thrombosis with other people ("controls") who are very similar in age, medical history, habits, etc., but who have not had thrombosis, and then to see whether or not there are equivalent numbers of Pill-takers in both groups. The crucial problem with such studies is the word "matching". Since we do not know all the factors which are at work in the thrombosis problem, it is impossible to match correctly for everything that might affect the comparison. Therein lies the great weakness of such studies. The widely quoted British study of Vessey and Doll falls apart on this very ground. After they had completed their efforts at matching, it turned out that the thrombosis group had a considerably different history with regard to previous thrombosis than the control group. To many statisticians this invalidates the study right there, since after-the-fact adjustments are not permissible. But even if this were acceptable, it now turns out that English women who take the Pill are, among other things, heavier smokers than women who do not take the Pill. Smoking itself has a definite effect on the frequency of thrombosis. Now the question arises, whether the differences attributed to the Pill in this study are not perhaps due to differences in the smoking habits of the two sets of subjects. Thus, at the very least, the conclusions of the British statisticians are open to question. There are many other technical reasons why this and the other British studies are held in doubt by many scientists; I had the privilege of being invited to discuss this question before a national assembly of biologists just last April. This is not the time or place to bore you with the technical details; the critical analysis of the British studies will appear in the scientific literature very shortly.

Almost at the same time that the British retrospective study was going on, a similar but considerably better-designed effort was underway in the United States. The American study avoided some of the pitfalls of the British study in

case matching. However, the American study also has serious drawbacks, which cause many statisticians to worry about the conclusions. One problem is shown in the following table:

RELATIVE RISK OF USING ORAL CONTRACEPTIVES, BY CITY (SARTWELL STUDY, 1969)

City	Number of matched pairs	Relative risk of thrombophlebitis (user/nonuser)	Statistical significance
Baltimore and Washington, D.C.	26	2.2	N.S.
Pittsburgh	25	3.0	N.S.
New York	83	4.2	P<.01.
Philadelphia	41	17.0	P<.001.

The American study included subjects from five large cities; they were supposed to be selected and matched in identical fashion. However, when one looks at the relative risk of taking pills in the different cities, something extremely interesting emerges. In Baltimore, Washington and Pittsburgh an increased risk, if it exists at all, could not be shown statistically. In New York, Pill-takers were clearly at four times the risk of thrombosis as non-Pill-takers, and in Philadelphia, Pill-takers were at 17 times the risk as the controls. Are we to conclude that people who want to take Pills should move from Philadelphia and New York to the other cities? Is there something mysterious about Philadelphia and New York that makes taking Pills there more risky? Or—as is more likely—is this simply internal evidence in the study that the matching was not homogeneous from city to city? If the latter is true—and this seems to be the most likely explanation—the validity of the whole work comes into question, since the very foundation of the retrospective study is shaken.

Although the British and the American studies concur in ascribing all risk of thrombosis to the use of the Pills, there are important differences which no one has as yet satisfactorily explained. The risk reported in British women is twice as great as that in the American study. Why should this be? The British found a three times greater risk in older women than in younger women; no such difference was found in the American study. The British study found an increased risk of cerebral thrombosis; the American study did not. Such inconsistencies do not increase our confidence in the conclusions of these studies, or in the applicability of British data to American women.

Nevertheless, it is a fact that a number of studies (all of the same sort, it must be admitted) concur in the conclusion that there appears to be some increased risk. Until proper studies are carried out and the truth of the matter is firmly established, it seems prudent to act on the assumption that a risk—a very small risk, it is true, but still a risk—exists. It therefore becomes important to assess this risk in the perspective of the risks that would face potential Pill-takers if they did not take the Pill. This leads directly to the next question.

Question 4. What is an acceptable risk of death from the Pill?

Answer: There is no simple answer to this question either.

There are those, of course, who say that noncontracepting women are healthy women, and that *no* risk is acceptable. This statement is incorrect from the start, since even the WHO definition of health states that, "Health is a state of complete physical, mental and social well-being, and not merely the absence of disease." Moreover, noncontracepting women are very much at risk—at risk of pregnancy: and pregnancy has associated with it a very real death rate. This death rate depends on social and economic status. Among our more privileged citizens, those who have access to good obsterical care, it is as low as 250 deaths per million pregnancies. In our underprivileged minority groups, the death rate is five times higher. Thus, in one year, of a million noncontracepting women 800,000 will end up pregnant, and 200 to 1,000 of these women can expect to die as a result of the pregnancy. How can anyone say that there is no risk without the Pill? There are, of course, other methods of contraception which carry with them no risk of death from the method itself. With the "rhythm method" there will be no "method risk", but lots of pregnancies—about 230,000 per million women per year, in fact. Of these 230,000 women, from 60 to 300 will die as a result of the pregnancy. The older mechanical devices such an condoms and diaphragms give better protection, but still 100,000 or more will get pregnant of a million women that use these methods. There will be no method deaths, but the deaths

due to these pregnancies will amount to 30 to 300 per year. Let us now look at the newer methods. The intrauterine device is much more effective than any of the older methods. Of a million women using it for a year, only about 50,000 can expect to get pregnant, and there will be only about 12–60 deaths from the pregnancies. But there are also deaths caused by the intrauterine device—a fact that its advocates like to play down. Indeed this fact is consistently omitted from the writings of the chief American statistician concerned with clinical trials of the IUD. It was brought to light by a survey conducted by the American College of Obstetricians and Gynecologists while the advocates of the IUD were busy looking at other things. The fact is, that there may be about 24 deaths per million users per year from the IUD itself. Then there are the deaths associated with the 50,000 pregnancies. Together, these two factors add up to about 40–80 deaths per million users per year. Now consider the Pill. It is far more effective than the IUD, and only about 10,000 pregnancies per million women can be expected. These pregnancies will cause 3–15 deaths. Now if the risk of thromboembolism is accepted at full face value, one may anticipate 12–24 pill-related deaths per million users, depending on whether the lower rate of the American studies or the higher rate of the British studies is accepted. Thus the total number of deaths, those from pregnancy plus those from the Pill; adds up to about 15–40 per million users per year—less than with any other form of contraception. These figures are summed up in in the following table:

THE RISKS OF PREGNANCY

[In a million reproductive-age women per year]

Pregnancies (number)	Deaths, total	Cause	
		Pregnancy itself	The contraceptive
No contraceptive (800,000)	200–1,000	200–1,000	
Rhythm method (230,000)	60–300	60–300	None
Diaphragm (200,000)	56–280	56–280	None
Condom (100,000)	28–140	28–140	None
Intrauterine device (50,000)	40–80	12–60	24
The pill (10,000)	15–40	3–15	12–24

Note: It becomes clear, when all the risks are considered, that taking the pill is the safest thing a woman at risk of becoming pregnant can do.

These figures show only the bare bones of the problem. They do not take into account the fact that healthy women who become pregnant against their will often resort to criminal abortion. The sickness and death from this awful alternative cannot even be calculated. Yet it is a known risk to the fertile woman who contracepts unsuccessfully. On top of all this, how can one measure, and how can one throw into the scales the anxiety, fear, frigidity, marital discord and infidelity that are generated by the fears of unwanted pregnancy and uncertain contraceptives? Perhaps such human values cannot be measured by statistics; perhaps our ivory-tower statisticians and biologists can ignore them, but the physician—the man who must deal with women-at-risk face to face—cannot. And they should count heavily in the scales of his judgment.

Some people have compared the death rate from drugs such as penicillin, digitalis, smallpox vaccination with the deaths allegedly due to the oral contraceptives. It may be argued that such comparisons are invalid, because these other drugs are taken to cure or prevent disease, and we have not yet come to consider pregnancy as a disease, even though it is sometimes fatal. Let it be agreed that taking Pills is a procedure elected by free choice by some women. How do the risks of this free choice compare with other free choices we make in our daily lives? If the death rate from the Pill plus the death rate from pregnancies associated with pill failure is 15–40 per million women per year, it is interesting to note that the death rate in women from smoking is 400 per million per year. Looking at it another way, the full claimed risk of the Pill itself is equivalent to the risk of a British woman smoking ⅓ of a cigarette per day, or of an American woman smoking a little more than 1 cigarette per week. Another thing we all do is to drive in cars. The death rate from traffic accidents of women of this age group is 370 per million per year. Some of us also like

to go motorboating. When father buys an outboard motor boat, he introduces a risk of death into the family which is ten times greater than that claimed as the risk of mother taking the Pill. It seems quite evident, that in our daily lives we knowingly elect to take far greater risks than that attributed to the Pill.

Still, when all is said and done, a finite risk may well exist. Who has the right to make the decision that some particular human being should or should not take this risk, no matter how small? This leads to our next important point.

Question 5. Should women be given information regarding the risks of the pill so that they can make their own decision?

Answer: In theory, yes; in practice, it depends.

Human beings are generally not impersonal decision-making machines. Emotions tend to color thinking, especially when life or safety is at stake. Thus there are innumerable sayings like "The doctor who treats himself has a fool for a patient". How coolly and objectively can a woman or her husband weigh information if they know that there is a risk of life or death—no matter how small—involved in the decision?

Aside from all emotion, making a sound decision requires having the necessary information and being able to evaluate this information correctly. It is certain that these Senate hearings have produced one piece of information about which no one can quarrel: that even the experts on this subject disagree as to the evaluation and interpretation of the available facts. These experts have years and years of education and training—more than a high school degree, more than a college diploma, more even than the degree of doctor of medicine. For some are specialists in clinical investigation, biology, or statistics. Literally centuries of experience have paraded before this committee—and there is no consensus among the experts. Is it then reasonable to suppose that a discussion between a physician and his patient, no matter how careful and well-intentioned, will, in 10 or 20 minutes so well inform the patient that she can now make a truly informed decision for herself?

On occasion I have had patients who discussed with me the various methods of contraception and then came back at a subsequent visit with the PDR in hand, and quizzed me about the Pill like a trial attorney. Such a patient needs and deserves every bit of cooperation and information the physician can give her, so that she can make a psychologically and intellectually acceptable decision. But how many women like this do you suppose there are?

Many women have heard that the Pill is the most reliable of all contraceptives, and they want to be as certain as possible that they do not get pregnant, and that's that. Is the doctor serving her best by trotting out a long list of statistical uncertainties, and making her anxious about a course of action she is already content with?

There are still other women, on or off the Pill, who have been frightened by the misinformation and distortions of the lay press. They deserve to have all the information they can understand and utilize. Unfortunately, few physicians have the powers of communication, as well as the exact information, to carry out this task as well as one would wish.

Finally, we must recognize that there are vast numbers of women who simply do not have inquiring minds like those that fill this room, and do not have enough education to comprehend much more than the simplest facts of biology. A misguided effort to "inform" such women leads only to anxiety on their part, and loss of confidence in their physician. They did not come for a lecture on statistics; they came for help in not having more babies. The doctor is the man who is supposed to know such things, and they want him to tell them what to do, not to confuse them by asking them to make decisions beyond their comprehension. The sound physician, by judicious questioning, can determine which contraceptive method is most likely to be acceptable and effective in a particular woman. This is the prime consideration. Then it remains to be determined if there are any medical contraindications to that particular method. But the idea of "informing" such a woman, so that she can make her own "informed" decision is pure nonsense that only a philosopher, an ivory-tower academician or a lawyer can dream up. In short, there is no general, dogmatic answer to the original question. *It all depends on the woman herself.*

Question 6. Who should give information to inquiring women?

Answer: Their physician, and no one else.

There are overwhelming reasons why this should be so. In the first place, it is by no means certain that a particular woman should use the Pill in preference to some other contraceptive device. If she is the type of person who cannot be

counted on to take pills reliably or if she "hates to take pills" in general, this must be known. Medical contraindications to taking the Pill can only be determined by a physician. It is also up to a physician to determine to what extent that particular woman is able to participate effectively in the decision-making process, and what amount and type of information she can successfully assimilate. The way in which this information must be presented to her will depend on her cultural and educational background. Thus, no prepared, stereotyped format will serve the purpose. On the other hand, it is perfectly plain that physicians are very busy people, and they are not usually communications experts or professional educators. Many patients complain that their doctors don't tell them anything even when they have a serious ailment. Now, when the advantages of a drug are as dependent on proper following of instructions as is an oral contraceptive, good communication and instruction become absolutely vital to acceptance and reliability. The pharmaceutical companies have prepared various booklets and memory aids to help physicians in this informational process. Presumably they have obtained the services of communications and educational experts to prepare effective instructional aids. However, even under the best of circumstances, such efforts represent a compromise, since one cannot design an instruction program for every educational level or cultural background. Thus, while physicians can use training and memory aids to great advantage, the ultimate task of information and instruction remains theirs, and cannot be delegated. In such measure as patients are not adequately instructed or informed, the responsibility rests squarely on the shoulders of the medical profession.

There is one other type of professional information which is widely available. This is the so-called package insert. Now, the package insert is supposedly a concise summary of significant information relative to a particular drug. In actuality it is no such thing. It is a guarded truce concluded between lawyers whose primary interest is to protect their drug company from lawsuits, and the bureaucrats of the FDA, whose primary interest is to make no decisions that can generate political intervention. In addition to this, there are the pressures of the company's marketing division, whose chief purpose is to make as many attractive claims as the lawyers and the FDA will let them get away with. Neither the medical profession nor their patients are well served by such a document, and it is quite understandable that many physicians place little value on it. One can hardly imagine to what extent the package insert can be misinterpreted by a layman who might get hold of one, and with the help of a medical dictionary, tries to interpret the technical language, unaware of the content in which it was generated.

Finally, I should like to comment on one other point:

Question 7. What is the proper role of the public information and communications media in this matter?

It is quite obvious from the scientific data themselves, as well as from the proceedings of many hearings such as this one, that the questions which have been raised and which justifiably concern each one of us, have not yet been resolved at the scientific level. If the scientists themselves cannot agree on the interpretation of the available information, it must be asked whether public discussion of these issue, scientifically unresolvable as they are at this time, can serve any purpose except to confuse and worry the public. It may be asked whether one proper role of the protectors of the public would be to encourage and fund scientific inquiries aimed at answering these questions; at forcing, if necessary, the drug companies and the governmental agencies to enter into joint undertakings for the solution of particularly difficult and expensive problems? It may also be asked, whether a responsibility of the protectors of the public interest is not also to identify and castigate irresponsible members of the communications industry who spread misinformation and give unjustified prominence to patently extremist opinions. Biased television reportage, daily emphasis on gore and violence, and distortion of medical information are all part of the same reprehensible, sensationalistic pattern. There is no question that much sincere and competent effort is devoted to informing the public, and the need for more was emphasized recently by the Hellman committee. Just two days ago, the Drug Information Association concluded a symposium in this city on "Drug Information for the Medical Profession." Let us hope this is a landmark for at least one aspect of the communications problem. But the other, that of competent public information, is yet untouched. Some years ago I was interviewed by a senior editor of Look magazine, and from the way he conducted the interview, I was

convinced that he was a Ph.D. in the biological sciences who was really up on his subject. It turned out that he was no scientist—but an extremely intelligent, well-read, and competent editorial writer. By contrast, we have the "uproar" articles of the newspapers and ladies' magazines, and the extremist views given undue prominence on television in England and in this country (See Appendix 2).

If this Committee is dedicated to finding out whether the Pill represents a safe and useful medical agent or an unmonitored, unacceptably risky drug being foisted off on the women of the world, I believe it should pay equal attention to the question of whether the media that are supposed to be the interface between medical science and the public are doing a responsible and helpful task or whether they are irresponsibly, unnecessarily and unjustifiably alarming the public by biased reportage. The irresponsibility even of national bodies has become a matter of great concern to scientists, as witness the response of the scientific community to the recent, wholly undocumented decisions of a British agency on the hormone dosage of certain Pills. In the December 20 issue of Nature, an editorial entitled: "How to alarm people and lose friends" stated: "It is something of a scandal that a government committee should . . . create cruel and wholly unnecessary alarm in the minds of some 700,000 women . . . The wisdom of making such an announcement without at least a summary of the (wholly unpublished) supporting evidence is open to question. . . ." It is already clear that the news media as well as some extremist scientists have swallowed this recommendation whole, as a proven truth, when in fact the evidence has never been presented for impartial scientific judgment. In this manner, news media and sensation-seeking individuals can parlay an unproven committee judgment into a panic cry for instant action. It is my sincere hope that this Committee will show calm and mature judgment in distinguishing facts from suppositions, and extremist viewpoints from sound deliberation.

APPENDIX 1.—EXTRACTS FROM THE BOOK, "METABOLIC EFFECTS OF GONADAL HORMONES AND CONTRACEPTIVE STEROIDS" (SALHANICK, KIPNIS, VANDE WIELE, EDS.)

Moos (p. 689): "On the average, women who were not currently on oral contraceptives complained more of a variety of menstrual and premenstrual symptoms than comparable women who were currently on oral contraceptives."

Gram and Gillette (pp. 90, 93): "The literature dealing directly with steroid effects on drug metabolism in vivo is inconsistent and difficult to interpret."

". . . from a standpoint of clinical toxicology, changes in drug metabolism are probably of the greatest importance only for those agents whose therapeutic index is low" (i.e. whose toxicity is high—therefore not the Pills)

"Moreover recent work has indicated enormous individual differences in drug metabolism by humans, and this would also tend to obscure the clinical significance of changes in the rate of drug metabolism."

Beck (p. 121): "Present evidence indicates that oral contraceptive agents are not as diabetogenic in man as pregnancy."

Spellacy (p. 124): Of 76 patients using a sequential oral contraceptive for an average of 7 years continuously, only a single one showed an abnormal GTT.

". . . both glucose and insulin levels were elevated and remained elevated for 24 months when a combination type oral contraceptive was taken. These returned to normal between 24 and 36 months of use for the group."

Gold (p. 732): "An elevation in the blood glucose during the estrogen-treated state may not, for all we know, be harmful to the individual."

Wynn and Doar (p. 171): retract their previous claim that oral contraceptives change certain blood fats possibly associated with atherosclerosis. Retractions of this kind are apt to cause some raising of eyebrows among scientists.

"The most important question of all, namely whether (certain) changes will accelerate the rate of development of atherosclerosis, requires extremely careful consideration. The evidence will be difficult to obtain and the answer may only become apparent in 20–30 years."

Furman (p. 255): "Thus it seems unlikely that the effects of sex hormones on serum fats can be offered by way of an explanation for the increased susceptibility of men to coronary heart disease."

Sandberg (p. 377) : "The effects of elevated unbound cortisol levels on human physiology, particularly when such levels are active over a very prolonged period of time as may occur in patients receiving contraceptive therapy *is at present totally unknown*" (italics ours).

Woods (p. 471) : "The large, carefully controlled prospective studies needed to define the association between oral contraceptives and hypertension *have not been published* and the information to date is largely anecdotal."

Luetscher et al. (p. 479) : "There is no proven connection between increased angiotensin generation or aldosterone production and high blood pressure in the patients. Similar rises . . . are observed in patients whose blood pressure does not rise to abnormal levels on the same medications."

Heaney (p 500) : "Thus estrogens . . . appear to stabilize the bone mass . . . Whereas they have not proved to be good treatment for osteoporosis, they may well prove to be very good prophylaxis."

Fletcher, et al. (p. 549) : ". . . hypercoagulability cannot be justifiably diagnosed, together with the implications of thrombosis predisposition, merely because coagulation factor concentrations are increased." "Taken overall, studies on blood coagulation changes in women on contraceptive medication indicate that . . . such medication induces changes similar to those seen in the pregnant woman at term but of a considerably more modest nature. On the basis of the present data, they would not appear to be significant in predisposing to thromboembolism."

Haslam (p. 642) : "However, while oral contraceptives and estrogens appear to increase platelet sensitivity to aggregating agents the difficulty of correlating these changes which occur in all women taking the pill, with the occurrence of thromboembolism in a very small minority, remains . . ."

Doll and Vessey (p. 575) : "If we conclude, as we believe we must, that the association (between pills and thromboembolism) is real, we have to consider whether it reflects cause and effect or is due to the existence of a common factor which is associated both with the use of oral contraceptives and with the development of disease. *In principle, it is impossible to decide this question on the sort of data we have been considering.*"

Seigel (p. 584) : "The estimates . . . of relative risk might account for an excess of 268 deaths in the U.S. in 1966".

By comparison, consider: if there were 6 million users at this time, no contraception would have resulted in approximately 1,800 to 5,000 deaths, or use of customary contraceptives in 300–1,500 deaths, as a consequence of pregnancy no longer prevented by use of the Pill.

APPENDIX 2.—EXAMPLE OF IRRESPONSIBLE AND INCORRECT INFORMATION PROPAGATED BY THE COMMUNICATIONS MEDIA

Statement.—Dr. Wynn on the David Frost Show, December 5, 1969—

> "I found unanimous condemnation of the Pill (in America). The Ford Foundation will not support this type of programme, neither will the Population Council, and the Rockefeller Foundation; they're all working toward new methods of contraception. Now if that is not condemnation of the oral contraceptive then I'd like to know what is."

Facts.—From "Contraceptive Technology", by Segal and Tietze of the *Population Council, October, 1969:*

"The outstanding advantage of oral contraceptives is their almost complete effectiveness."

"Available observations have failed, as yet, to establish or to exclude a statistical association with oral contraception for most of the adverse experiences reported in the literature. The one important condition for which an association has been established is thromboembolic disease . . . the excess mortality from pulmonary embolism attributable to the OCs may be estimated at 3 deaths per year per 100,000 users. The significance of this mortality should be weighed against a risk to maternal life resulting from or associated with pregnancy and delivery—exclusive of illegal abortion—of about 25 per 100,000 pregnancies."

"Nevertheless, since the OCs have proved themselves far superior to the traditional methods among low-income groups in the developed countries, it may be expected that they will also be more useful in the developing countries."

Fact.—The Population Council supports the research of Dr. William Spellacy, who presented his latest data at a meeting which Dr. Wynn personally attended in 1968. The published report of these proceedings, which include a presentation by Dr. Wynn, clearly and explicitly acknowledge Dr. Spellacy's source of support.

CURRICULUM VITAE

Joseph W. Goldzieher, M.D., Director, Division of Clinical Sciences, Southwest Foundation for Research and Education, San Antonio, Tex.

Date of birth: September 21, 1919.

Place: Budapest, Hungary.

Education: Harvard University, A.B., 1940, Chemistry (cum laude); New York University College of Medicine, M.D., 1943.

Present positions: Research professor, Trinity University, San Antonio, Texas, 1959–69; Senior Foundation Scientist; Director, Division of Clinical Sciences; Chairman, Department of Endocrinology, Southwest Foundation for Research and Education, San Antonio, Texas—1957–present; National Consultant to the U.S. Air Force (Department of Medicine, Wilford Hall Hospital), Lackland Air Force Base, Texas—1960–present; National Consultant to the U.S. Army (Department of Medicine, Brooke General Hospital), Fort Sam Houston, Texas—1956–present; Private practice of Endocrinology, 1947–present.

Previous position: 1943–1944, Internship in Medicine & Surgery, Bellevue Hospital, New York City; 1944, Assistant Residency in Pathology, New York City Hospital; 1945, Residency in Dermatology, New York City Hospital; 1945–1946, Postgraduate Residency in Endocrinology, Duke University Hospital; 1948–1953, Consultant in Endocrinology, various hospitals, New York City, Department of Health; 1949–1953, Research Director, St. Clare's Hospital, New York, New York; 1953–1957, Head, Endocrine Section, Southwest Foundation for Research and Education, San Antonio, Texas.

Professional Societies: Fellow, the American College of Clinical Pharmacology and Chemotherapy; Diplomate, American Board of Clinical Chemistry; Associate Fellow, American College of Obstetricians and Gynecologists; Fellow, New York Diabetes Association.

Member: The Endocrine Society; Mexican Society of Nutrition and Endocrinology; Laurentian Hormone Conference; American Fertility Society; Pacific Coast Sterility Society; American Association of Clinical Chemists; Association of Harvard Chemists; American Medical Association; WHO Committee on Antifertility Steroids.

Publications: Approximately 250 to present, on research related to endocrine (especially steroid) methodology, adrenal and ovarian disorders, steroid metabolism, reproductive physiology (both clinical and experimental), and fertility control both clinical and experimental.

Numerous papers devoted to the development and evaluation of oral and injectable contraceptive.

Senator MCINTYRE. Thank you, Doctor.

You have just stated that you have been present at sessions where the wording of the package-insert labeling is worked out between FDA officials and representatives of the manufacturers of the pill. In what capacity, Doctor, were you present at such meetings?

Dr. GOLDZIEHER. I was asked there as an expert, and my job there was not to be involved in this aspect; I happened to be a bystander. I was there in an effort to help the FDA and the company come to some agreement as to the experimental designs which would answer the questions that were troubling the FDA regarding safety or efficacy.

Senator MCINTYRE. At whose request were you present?

Dr. GOLDZIEHER. I was present at the request of various drug companies at various times.

Senator MCINTYRE. Have you, as a matter of fact, ever served as an investigator for any of the companies which market oral contraceptives?

Dr. GOLDZIEHER. Senator McIntyre, I serve as an investigator for the National Institutes of Health, the National Science Foundation, the Southwest Foundation for Research and Education. I am a consultant to the U.S. Air Force and to the U.S. Army, and I am a consultant at various times to various drug companies.

Senator MCINTYRE. And you receive remuneration from the drug companies for this work?

Dr. GOLDZIEHER. Among others. Also from the Air Force, the Army, the Southwest Foundation, and also from my patients, I might add.

Senator MCINTYRE. I don't wish you to take any umbrage or any offense at this line of questioning, because you mentioned it, and it is a problem to try to get what we would call unbiased testimony.

Now, the major thrust of the early part of your testimony, Doctor, as I understand it, is that the questioning of patients concerning their experience with the pill is not a highly reliable way to determine the frequency of side effects, is that correct?

Dr. GOLDZIEHER. With certain reservations, yes.

Senator MCINTYRE. But is it not a fact that the really serious potential effects of the pill, such as thromboembolic disease or carcinogenisis are not the kinds of conditions which could be detected through this kind of subjective response?

Dr. GOLDZIEHER. There are two classes of side effects that we have to deal with: those which occur with some degree of frequency, like nausea, which can be evaluated by fairly simple statistical designs. There are extremely rare side effects, such as thromboembolic disease, which are not picked up by this type of study.

Now, what is the process by which such a rare condition as thromboembolic disease can be picked up? There are two aspects of it.

First of all, somebody has to say, "I had a patient who developed something or other, and I wonder if it was related to the fact that they were taking an oral contraceptive?"

This is a raw adverse-reaction report of a rare, perhaps lethal, event in a woman taking a particular drug, oral contraceptive or otherwise. Reports of this kind are a raw material, an unevaluated raw material, because they are in effect a numerator without a denominator, and the only purpose of such reports—though unfortunately it is not the only purpose to which they are put—is to alert us that here is a matter for concern, and that it is required that we now sit down and devise an experiment, a study, an investigation, a protocol, which will enable us to reach a conclusion which is statistically meaningful as to whether this was or was not coincidental.

Senator MCINTYRE. I take it that you agree generally that the testimony you gave relative to side-effects complaints and their unreliability still does not depreciate one bit the fact that the most serious things that are worrying some of us are really not developed under a side effect sort of complaint.

Dr. GOLDZIEHER. If you mean the metabolic effects, obviously, metabolic effects are not developed by questioning.

Thromboembolic disease turns up because you follow the patient. She will tell you yes, she has a pain in the calf, and you find a thrombophlebitis. You will turn it up if the patient does not show up at the

clinic, and you place a phone call to her home and you find she has been hospitalized. So questioning does turn this up to an extent, though.

Obviously, never to 100 percent.

Senator McINTYRE. Moving on with respect to the animal studies linking estrogen to cancer, you point out that the first experiments were performed on highly inbred strains of mice. As I understand it, most animal experiments are performed on pure breeds to assure reliability of results. Is there any evidence that this particular breed of mice was unusually susceptible to cancer?

Dr. GOLDZIEHER. Yes, sir. The Lacassagne studies in the 1930's used a highly inbred strain of male mice, as a matter of fact, and those experiments were complicated by a fact, then unknown, which was that there is a virus which is transmitted in mouse milk, which causes breast cancer. This raises serious problems with the whole studies.

The reason that pure bred strains of mice are used is not only because you get better experimental designs and better results with smaller numbers, but also because if you use a strain of mice which does not develop the cancer, you have spent a lot of time doing nothing.

Senator McINTYRE. Is there any evidence, Doctor, that the other four breeds of animals in which a relationship between hormones and cancer has been established were unusually susceptible to cancer?

Dr. GOLDZIEHER. The dog breast—the dog, as a matter of fact, is exceptionally susceptible to estrogens. In the dog you can destroy the tubes from the uterus to the ovary, by the administration of estrogen. It is a unique susceptibility. As a matter of fact, I might add that the beagle which is now——

Senator McINTYRE. The beagle?

Dr. GOLDZIEHER. The beagle, which is now being used and which is the basis of the present problem with the mini pill, the beagle is an especially susceptible breed of dog.

Senator McINTYRE. The other three?

Dr. GOLDZIEHER. I don't know at this moment exactly which strains of rabbits were used. You can vary the strain. You can vary susceptibility in any animal for anything you want by appropriate inbreeding.

Senator McINTYRE. It seems to me you are suggesting that Dr. Hertz, who testified here last week, may be less than objective on the subject of the relationship of hormones to cancer. It seems to me, Doctor, that he came to the same basic conclusion as you; namely, that we still do not know whether the animal studies linking hormones to cancer are relevant to human experiences.

However, do you know, Doctor, of any reason why Dr. Hertz would be biased in this matter?

Dr. GOLDZIEHER. I don't think I care to speak for Dr. Hertz. He is too good a friend of mine to debate with when he is not here. He and I have debated this, and I have my own thoughts on the subject, but I think it would be unfair to present them here.

Senator McINTYRE. You don't know of any reason that he would be biased?

Dr. GOLDZIEHER. It depends on what you mean by biased. If you mean opinionated, yes, he is.

Senator McINTYRE. On the bottom of page 6 of your statement, you point out that although estrogen has been in medical use for 35 years, there is no evidence that they have contributed to the incidence of cancer.

First of all, let me ask you whether there has been any increase in the incidence of cancer during the past 35 years?

Dr. GOLDZIEHER. There has been an incidence in breast cancer in this country. I can't give you the figures. This has been summarized by some of Dr. Segaloff's reviews. This incidence has also occurred in women who have never taken estrogens, particularly in young women. We are seeing an increase in breast cancer, so I understand.

Senator McINTYRE. You have specified breast cancer. Has there been any rise in the rate of cancer in other forms?

Dr. GOLDZIEHER. I couldn't tell you at this moment.

Senator McINTYRE. Anyway, it seems to me there are a number of difficulties with the table you cite to support your position. First of all, the table is dated 1963, shortly after the oral contraceptives came on the market, and although there is no way of identifying the years covered, they certainly would represent a period in which the estrogen was not being used in even the tiniest fraction of the 8½ to 9 million estimated to be taking it today.

Secondly, in three of the five studies cited, the expected number of cancers appeared to be based purely on the investigator's estimate, and we have no way of knowing how reliable that might be.

Finally, Doctor, there are no distinctions as to types of cancers or distribution by age, or sex, or any number of other factors which might very well be relevant. Would you care to comment on that?

Dr. GOLDZIEHER. Yes. I think you are practically quoting Dr. Hertz verbatim. I carefully said that these studies are not conclusive. I will agree that they have many objections, some of which you have stated. I am simply trying to point out that what available information there is, inadequate as it may be, whatever information may be gained from the fact that women have been treated with estrogens at some dose, which is certainly closer to the oral contraceptives than the dose which is used in the animals to produce breast cancer, that all this body of evidence which should have turned up something—just as an interest in thrombophlebitis did turn up something in a relatively few years—this body of evidence on menopausal and other estrogen-treated women so far has not turned up anything.

Senator McINTYRE. Doctor, does it take a great deal longer for cancer to show up as opposed to thromboembolic diseases?

Dr. GOLDZIEHER. We estimate a 10-year period or more.

Senator McINTYRE. For what? For cancer?

Dr. GOLDZIEHER. For cancer. Since we don't know the cause of idiopathic thromboembolic disease, I don't know how long the factor has been there, so I cannot give you any estimate at all of what the duration of predisposing factors is in thromboembolic disease.

Senator McINTYRE. Now, on page 7 of your statement, you say, "There are, if anything, less tumors occurring in women on hormones than in those taking no hormones at all."

On what evidence do you base your testimony?

Dr. GOLDZIEHER. I am referring to the table.

Senator McINTYRE. You are referring to the table?

Dr. GOLDZIEHER. The table of the 1963 summary, showing the observed number of tumors and the estimated number of tumors which would have occurred in a group of that age distribution with no treatment at all. I am not trying to make a point of the fact that there were less tumors. You could not support this statistically, and I was careful to say so. I simply used the table for one point; namely, that what information there is does not support Dr. Hertz' worry.

Senator McINTYRE. What you are also admitting is that the statistics are not really conclusive.

Dr. GOLDZIEHER. Most certainly not conclusive.

Senator McINTYRE. You say that Dr. Hertz objects to these figures on the ground that they refer to older women, and that a younger age group is on the pill. And you take exception to this on the grounds that there is no proof that the two age groups are any different in their susceptibility to cancer.

Ironically, Dr. Kistner, who testified last week and who seems to agree with you on almost everything else, took Dr. Hertz to task for quite the opposite reason.

As I recall, Dr. Kistner said Dr. Hertz did not allow for the fact that, at least with respect to breast cancer, there is a difference in susceptibility between the older and younger age groups. Now, do you disagree with Dr. Kistner?

Dr. GOLDZIEHER. Let me say that I cannot understand on what he bases that statement since, (1) we do not know the latent period; (2) we do not know the predisposing factors; and (3) we do not know—as a recent virologist from New York proposed—whether people are born with the virus which causes their cancer, and something simply brings it out at some particular time. I think the honest answer to this is that Dr. Kistner and I are both speculating.

Senator McINTYRE. Doing what?

Dr. GOLDZIEHER. Speculating.

Senator McINTYRE. I take your answer to say that for lack of further information you do disagree with Dr. Kistner?

Dr. GOLDZIEHER. No; I think neither of us know.

Senator McINTYRE. On page 7 of your statement, you commented extensively on a recent study emanating from New York City concerning the relationship of cancer of the cervix and the pill. Are you referring to the study by Melamed and Dubrow?

Dr. GOLDZIEHER. Yes.

Senator McINTYRE. You say that this paper was of such poor scientific quality that it was rejected out of hand by scientific editorial review in this country. Would you please tell us how you know this?

Dr. GOLDZIEHER. I don't know whether I am at liberty to reveal private discussions I have had with individuals who are associated with the editorial department of the AMA.

Let me simply say that if you were to take the published report as it appeared in the British Journal, and if you asked me, or better, a number of cancer specialists who are familiar with the problems of cancer of the cervix, whether they would accept this manuscript as a piece of sound scientific work which permits of conclusions, I would venture to predict that most of them would turn it down as

proving nothing. As a matter of fact, Senator, I might point out that as the paper finally did appear, they were very careful to say that the paper proved nothing.

Senator McINTYRE. I am informed by the committee staff here that accounts appeared in both the general and trade press with reference to this study. It was rejected by the Journal of the American Medical Association, not out of hand, but only after many months during which the authors and the editors were unable to agree on the revisions.

Dr. GOLDZIEHER. Which would suggest that it was initially unacceptable to the AMA, would it not?

Senator McINTYRE. You say that this study finally managed to get itself published in an English journal noted for its lack of editorial discrimination. Was it not published, Doctor, in the British Medical Journal, which is the official organ of the British Medical Society and the counterpart of our own Journal of the American Medical Association?

Dr. GOLDZIEHER. It is the official journal of the British Medical Society. That does not necessarily give it a superlative scientific caliber.

Senator McINTYRE. Does this statement, the statement that this journal—I am now referring to the British Medical Journal—this journal is noted for its lack of editorial discrimination, represent simply your own opinion, or is it based on some evidence?

Dr. GOLDZIEHER. No, sir. It is my opinion exclusively, and it is based on the fact that this particular journal publishes large numbers of letters of an anecdotal nature, which are perhaps amusing, but are of dubious scientific merit, but which are then used for purposes which are not admissible. Having crept into the scientific literature as information—any statistician would call it anecdotal information—it then gets quoted and requoted. This is of questionable value to the medical community.

Senator McINTYRE. Doctor, is it not true that letters to medical journals might very well be a manner and a way of detecting problems that may be occurring?

Dr. GOLDZIEHER. I think there are better ways, Senator. There are all kinds of systems set up for adverse-reaction reporting, where the information is not made public, but privately and scientifically pooled in the hands of a body that knows what to do with such data. To take such raw data is like opening the FBI files, which have probably everything on everybody anywhere that he ever said, some of which may be true, some of which may be false. This raw information should not, in my opinion, appear in a journal of this type. It should go to a body like the FDA; it should go to a body like the Tissue Reaction Committee of the Armed Forces Institute of Pathology. It should go to some body which knows what to do with this information. Printing it in the British Medical Journal is no way to handle this kind of information.

Senator McINTYRE. Dr. Goldzieher, on page 8 of your statement you say there has been a rapid increase in deaths from thrombosis of unknown cause since 1958 in both men and women, and you cite a British study of fatal pulmonary embolism in support of your statement, and point out that the increase began before use of the pill was widespread, and that none of the victims were on the pill.

Looking at the chart, I can see that the increase did begin before the use of the pill became widespread, but the really dramatic part of the increase has occurred since 1962. Therefore, this increase does in fact parallel quite closely the increase in the use of the pill.

I can see some other difficulties with the chart in that it makes no distinction by sex, age, or any other factor. However, the thing that really strikes me is that there were no pill users at all among those victims.

Does this not seem a little strange in view of the large numbers of women taking the pill during much of this period?

Dr. GOLDZIEHER. I can only accept the statement as it appears in the British literature.

Senator MCINTYRE. You can't tell us how it was determined that none of the victims were using the pill?

Dr. GOLDZIEHER. I can only refer back to the original document and go through it with you, word by word.

Senator MCINTYRE. Did this information come from the British Medical Journal?

Dr. GOLDZIEHER. I don't remember. I would have to look up the reference.[1]

Senator MCINTYRE. I would like you to supply it for the record.

Dr. Goldzieher, where did you obtain the statistics contained in the table on page 12 concerning unwanted pregnancies and deaths associated with different types of contraceptives?

Do you know how these statistics were derived and how accurate they may be? Do you think that they are any more reliable than those in the British study, and the Sartwell studies, of which you were quite critical?

Dr. GOLDZIEHER. Senator, I think Dr. Hellman attempted to answer this question, and I can only echo what he said. The numbers themselves are clearly ball-park figures, since the difference between higher socioeconomic and lower socioeconomic level is a factor of five, so that you can take any population of a socioeconomic status anywhere in between there, and arrive at any particular number you choose.

You can find such calculations in Dr. Potts' book. You can find calculations such as this in a publication by Drs. Segal and Tieze in one of their recent "Reports on Population/Family Planning," October 1969.

They are not difficult to obtain from any text which gives approximate frequencies for failure rates, for the various contraceptive methods.

Senator MCINTYRE. Any text? You are referring us to any text that deals with this subject? Are there any publications?

Dr. GOLDZIEHER. There is a book by Dr. Potts, which Dr. Wynn just had on the table here, which he took to task. I believe that table will be in there. I believe the same table is in Dr. Potts' publication from the Fourth Asian Congress of Obstetrics and Gynecology, pp. 151–159.

Senator MCINTYRE. I just comment to say that these figures that I have produced here on page 12 don't seem to jibe with any that we have received from Dr. Hellman, but I want to thank you very much, Doctor.

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[1] Dr. Goldzieher subsequently supplied the following reference: "C. A. Loehry, Brit. Med J., 1: 1327–1328, 1966."

Senator Dole?

Senator DOLE. Thank you, Mr. Chairman. I have only a few questions. I regret my absence, but we were doing something in Agriculture which required my presence.

First of all, I note in your statement you had widespread experience in the research and clinical fields. I wonder how extensive this has been. Have you had a chance to observe side effects, if any, that are caused by the use of the pill?

How many patients have you had, how many people have you seen?

Dr. GOLDZIEHER. I cannot give you any estimate as to the number of private patients with whom I have worked on the problem of contraception.

I can tell you that in our research clinic, which I monitor constantly with Dr. Moses, who is the immediate chief, and where we analyze all these statistics and all the side effects every month, we started since November 1958 and now have 3,500 monitored patients and over 100,000 cycles of experience.

I have been consultant monitor for collaborative clinical trials; just to mention one: we have over 350,000 cycles of experience. The computer printouts are made available to me every time a new run is made. I am asked then to comment on the statistical analysis.

I have also collaborated on other smaller trials, most of which have been published, and as I think I pointed out on page 1, since we first started publishing in 1960, there are approximately 62 publications from our group in the literature on this subject of oral contraceptives.

Senator DOLE. I think the thing that concerns me, and I am certain other members of the committee, I have heard witnesses today with divergent views.

I read your testimony. Then I look back at the testimony of Dr. Williams. I am just wondering what we can expect, how we can expect the American female to react after reading both your statement and his statement. I mean, they are almost as far apart as you may go. How do we properly inform the American public when we have such divergent views?

Dr. GOLDZIEHER. Senator, I think this is the crucial question in this whole matter, and the factors that we must recognize are these:

Since the best medical judgment available today cannot agree either on the existence of some of the risks or on the magnitude of the admitted risks, we cannot falsely alarm the American woman.

On the other hand, it is incumbent on us not to falsely reassure her that she can really go on forever taking the pill.

As I tried to point out in my testimony, the answer is one of perspective. What are her alternatives in making her individual decision? To me the crux of the matter, the unacceptable alternative, is the higher failure rate with other contraceptives. I cannot fathom how Dr. Hellman or others have said that obstetrical deaths are probably irrelevant. I find it very difficult to swallow the fact that dead women are irrelevant. I find criminal abortions very relevant. I find unwanted babies very relevant. And until somebody can show me that for a particular woman I have not prescribed what in my best judgment is the best contraceptive method, I must stand on my position.

Senator DOLE. On that basis, then, do you foresee something replacing the pill or an improvement in the pill? There is not absolute safety

in anything, but do you see improvements being made right along, and what should be the role of the FDA in all of this?

Dr. GOLDZIEHER. Well, sir, there was an article some few months ago by Carl Djerassi in Science, which pointed out a critically important fact; namely, that it will probably depend on the United States—which has the people, the technology, the money—to lead the world in the development of better contraceptive methods. The problem that has been generated, Senator, is that the present restrictions on research, which have been promulgated by the FDA, are so prohibitive both in practicality and in cost that they are going to shut off a lot of the potentially useful contraceptive research in this country.

I can tell you personally that a company as large as Du Pont withdrew from our clinic the testing of a new compound, because they considered it prohibitively expensive under the current FDA regulations.

I can tell you that under the current FDA regulations the development of another promising compound is being delayed and may never come to fruition, because a company has to think whether they can afford to spend that much money on a product which is far from the point where it looks as if it might make the grade. We know that, of 100 compounds that get screened, not 10 percent will ever make the grade.

I am terribly concerned that good clinical research in population control methods is going out of this country, because it is becoming impossible to run clinical trials here because of restrictions and expense. I feel very strongly that we need a new orientation and fresh blood to solve this whole problem.

At the Senate meetings on S. 2108, Senator Tydings' bill to establish a National Center for Population and Family Planning, I suggested that such a Center or its equivalent should take over the FDA's responsibility for development and monitoring of safety and effectiveness of all contraceptive methodology, and that it should not be subject to the unfortunate mechanisms which hamstring this agency today.

I think for someone who is concerned with the population of the world, and the pollution problems and the environmental problems that Senator Nelson spoke about, nothing can be more urgent than to take a really careful look at whether the good intentions of the present FDA mechanism are not in fact the greatest obstacle we have to contraceptive development, and whether unwittingly the FDA now is the Vatican's best ally.

Senator DOLE. I certainly assume that everyone who appears here are men of honesty, integrity, concerned about the public health, welfare, and all these things, but I find it almost impossible to reconcile the testimony, your testimony, with testimony of, again, Dr. Williams and other testimony, where almost completely opposite views—perhaps you are the pro-pill witness and Dr. Williams anti-pill and Dr. Wynn somewhere in the middle.

A woman perhaps sitting in the audience, trying to decide whether or not to take the pill today, will certainly be confused by this. How do you reconcile this, and how do we, as laymen?

We are not experts. I think you point in answer to question 7 that the best person to ask about the pill is your doctor.

I assume by this you mean that you just can't put it down in some simple printed form that fits every woman in America, because of the very reasons you state, but how do we reconcile this, as average Americans, whether the pill should be taken or not taken, when we have these conflicting statements?

Dr. GOLDZIEHER. Well, part of the conflict, Senator, is due to the fact that there are cases of anything which are due to coincidence, and no one can say Jane Doe, who was on the pill and had a coronary, had that coronary because she was on the pill. No one can say it in that particular case.

If you take a woman who was on the pill and who then has a pulmonary embolism and dies, according to Dr. Sartwell's own figures, the chances are three out of four that her pulmonary embolism was not related to the pill. Therefore, how can you say whether that Jane Doe's pulmonary embolism was one of the three that was unrelated to the pill or the one that was?

Therefore, what statistically we call anecdotal information—case reports—are not the subject of sound scientific decision. When somebody corners me in the hall and says, "I have seen a case of so-and-so," I turn him off.

As a person, I may be very concerned, but, scientifically, this is not particularly useful information—though it may sell books or magazines—and we cannot make scientific decisions on information of that kind. And we should not scare the American woman by case reports, because she is not getting honest, usable information. She is getting anecdotes, and we have got to separate anecdotes from information.

Therefore, I can only say that we must rely on the scientific debate, which should go on behind closed scientific doors, like a Harvard conference which produced a fine book; like the FDA reviews from time to time. Only in this way can we come up with valid information which will replace my opinion if I am wrong, or somebody else's opinion if they are wrong.

Senator DOLE. But based on the information available to you and to anyone else at the present time, you see no great danger then in continuing the pill, if you are taking it with proper medical supervision?

Dr. GOLDZIEHER. I still feel that, considering the dangers of obstetrical death, the pill is today the single safest thing that a woman at risk of pregnancy can use; I said so in my testimony and I repeat it categorically at this time.

Senator DOLE. Now, with the patients you treated yourself, I know you have discussed with charts, different side effects, and whether or not they were present, and whether or not they were related to the pill.

Is there any one side effect that you have personal knowledge of, that you have observed after months with the pill, nausea or any of the other things that are mentioned? What would you say the side effects of the pill are that we can put our finger on?

Dr. GOLDZIEHER. The inconvenient essentially minor side effects are the ones that trouble up to 10 percent of women: nausea, weight gain, general feelings of ill-being. These are largely inconveniences. Often, if a woman can really afford another pregnancy, like a doctor's wife, she is the one that is going to complain bitterly about these inconveniences.

But poor Mrs. Gonzales who has 10 children, and cannot afford the 11th—she will not complain. She may be afraid that if she does complain, they won't give her the free pills. This is one of the ways biases creep into the data.

Senator DOLE. Thank you.

Senator MCINTYRE. I want to thank you very much, Dr. Goldzieher, for being here and taking the time to be here.

Before we adjourn, at the suggestion of the chairman, that in view of appendix 2 to Dr. Goldzieher's statement, entitled "Example of Irresponsible Information Propagated by the Communication Media," which it makes reference to you, Professor Wynn, if you would like to have the opportunity to return to the witness table to respond to these comments, we would be happy to have you.

STATEMENT OF DR. VICTOR WYNN—Resumed

Dr. WYNN. Senator McIntyre, thank you for inviting me to return to the table to comment on appendix 2, which was submitted by Dr. Goldzieher as a part of his testimony.

It would be, in fact, quite difficult for me to comment upon this appendix without discussing quite a bit of Dr. Goldzieher's testimony, but I don't intend to do this.

It is obvious that I don't agree with many of the statements that Dr. Goldzieher made, and I would have no difficulty, in my view, of refuting many of the statements that he has made, but I do intend to refute the statement, as an example, of irresponsible and incorrect information propagated by the communications media.

I made that statement when I was in New York, visiting the Population Council and the Ford Foundation, which I have done, to my recollection, three times in the past 3 years, that I found there a great deal of uneasiness about oral contraceptive medication, and a lack of enthusiasm for the medication, and I was trying to express this in this statement, which, of course, has been taken entirely out of context, and what I would recommend is this:

That a witness from the Ford Foundation, and I would ask that Dr. Southam be considered, and a witness from the Rockefeller University, Population Council, and here I would recommend Dr. Shelton Segal, be invited to testify, and I would be very satisfied if during the course of the testimony—of course, I will not be here, regrettably—but I will be very satisfied if you would ask both of these individuals whether in the last year or so I have discussed at length with them their attitude and attitude of their foundation to oral contraceptive medication, and whether I was entitled to draw the conclusion that neither of these extremely important foundations, whose main interest is in the field of population research and population control, whether I was entitled to draw the conclusion that I did, that they considered oral contraceptive medication an unsatisfactory way for the world to control this problem of excessive fertility.

Senator MCINTYRE. I will refer the suggestion to the chairman of the committee.

The committee stands in recess until 9:30 tomorrow morning.

(Whereupon, at 6:05 p.m., the committee adjourned, to reconvene at 9:30 a.m., Friday, January 23, 1970.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

FRIDAY, JANUARY 23, 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. Come to order, please.

Our first witness this morning is Dr. Hilton Salhanick. Dr. Salhanick, we are very pleased to have you here this morning. Just take a seat.

Would you like to just put a brief biological [laughter] both biological and biographical statement into the record, biographical first?

STATEMENT OF DR. HILTON A. SALHANICK, PROFESSOR OF OBSTETRICS AND GYNECOLOGY, HARVARD UNIVERSITY

Dr. SALHANICK. My name is Hilton Salhanick. I am professor of obstetrics and gynecology at Harvard University. I hold appointments in the center for population studies and the department of population sciences in the school of public health and the department of obstetrics and gynecology in the medical school.

I have been asked to discuss the chemical and biological activities of the contraceptive steroids.

Senator NELSON. Your statement will be printed in full in the record, and if you wish to elaborate, extemporize on any aspects as you go along, feel free to do so, and I assume you will have no objection if we ask you questions as they occur to us.

Dr. SALHANICK. I would be delighted.

I accept this assignment with a sense of considerable responsibility because of the large number of couples who are currently dependent on these drugs for contraception.

In December 1969 under the sponsorship of the Center for Population Research of the National Institute of Child Health and Human Development and the Harvard Center for Population Studies, a con-

ference was held in Boston to enumerate and discuss the metabolic [1] effects of the contraceptive steriods. Approximately 75 persons participated in that conference, including representatives of various foundations and Federal agencies of the United States. Most of what I have to say is derived from proceedings of that conference and, in a general sense, is summarized in the preface to the book, "Metabolic Effects of Gonadal Hormones and Contraceptive Steroids."

These alterations, which have been demonstrated, include changes in carbohydrate metabolish, fat metabolish, protein metabolish, and the endocrine, liver, nervous and vascular system, among others. The findings are straightforward and reproducible. The implications and interpretations of the laboratory and clinical findings, however, are not yet resolved.

Certain facts are clear. First, the contraceptive steriods are not natural substances and should not be identified as such. They are unique, synthetic compounds, each with its own spectrum of activity, and regardless of dose, route, and frequency of administration, their effects cannot be equated with pregnancy, pseudopregnancy, or various phases of the normal menstrual cycle. I believe that the semantic oversimplification which equates the pharmacological state induced by the contraceptive steroids with biological states such as pregnancy should be abandoned.

Second, contraceptive steroids are not "equal." They are not all the same.

Senator NELSON. May I interrupt a moment?

Dr. SALHANICK. Yes, sir.

Senator NELSON. In your sentence, "I believe that the semantic oversimplification which equates the pharmacological state induced by the contraceptive steriods with biological states such as pregnancy should be abandoned," in what ways are they different?

Dr. SALHANICK. Well, they differ in some hormonal levels which occur. They differ in the some of the biological responses which occur. They differ in the ratios of the estrogenic and progestational substances and in many of the fine descriptions of the chemical changes in the blood.

The contraceptive steroids are not "equal." They differ both in chemical structure and in biological function. Modern chemistry has synthesized a vast array of steroid molecules and has produced a comparatively thorough understanding of their metabolic functions. The limited structure-activity data available appear to indicate that it may be possible to separate some of the metabolic effects from the contraceptive activity. To my knowledge, however, no steroid with contraceptive action has been demonstrated to be of all metabolic effects. I see the development of such a substance as one of the very difficult challenges of the future.

Not only do the contraceptive steroids differ qualitatively, but there are probably different dose-response relationships. This is an important aspect of the problem if we anticipate the development of new steroids with minimal side effects. It is of interest that after more than 10 years of use, the dose-response curve for contraceptive effective-

[1] Metabolism: The sum of all the physical and chemical processes by which living organized substance is produced and maintained * * *, and also the transformation by which energy is made available for the uses of the organism * * *. Dorland's Medical Dictionary, 23d ed.

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

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

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

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

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

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

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

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

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

Hopefully, such a program would identify those substances which may be safe and those which may be of concern. It might identify those women who are most susceptible to the adverse effects of the drugs. And, it might identify those complications which may occur after long-term use.

On the other hand, I do not anticipate that solutions to these problems are near at hand. Epidemiological studies and long-term clinical studies are hampered by the variety of drugs available, the intermittent consumption of the drugs, the mobility of our population, the variable durations of therapy, our lack of knowledge of what endpoints to search out, and last, but not least, our lack of knowledge of the true incidences of many of the diseases which might be involved.

Almost 10 years elapsed from the first reports to the final conclusion by the British epidemiologists that the contraceptive agents were implicated in thromboembolism. In that instance, there is approximately a fivefold to tenfold increase in risk. It may require an equivalent period of time to detect as much as a doubling of risk for some of the other hazards. Fundamental investigations aimed at the basic understanding of the functions of the substances, by their very nature, are of long duration.

In view of these possibilities, we are faced with a dilemma. I am convinced that, for some couples, there is no adequate substitute for the contraceptive agents. I am equally convinced that, for others, the type of contraception employed may not be an important consideration. I believe, therefore, that we should pursue an intermediate course, and while temporizing measures may be desirable, we must acquire as rapidly as possible as much information as we can. Accordingly, I urge the initiation and continuation of a broad range of studies. Enough support must be forthcoming to avoid the monopolies of limited-research approaches or narrow concepts. The scientific community must be encouraged to range widely and freely in studying the effects of the contraceptive steroids, and in the other areas of contraception as well.

Senator NELSON. Who do you suggest should initiate and direct the kind of research you refer to?

Dr. SALHANICK. I think there should be at least three sources of stimulation of the investigative effort. First, I think, the control agencies should initiate certain of the research endeavors.

Senator NELSON. To whom do you refer when you say control agencies?

Dr. SALHANICK. The FDA.

I think the National Institutes of Health should initiate, continue, and support some of the research efforts, and I think that there should be funding of research in universities which are not doing direct research projects, but are instituted from the creative minds of the individuals there. In addition, I think that industry has the responsibility to continue some of their investigation.

Senator NELSON. Have you done any metabolic studies yourself on the effects of the pill?

Dr. SALHANICK. No, sir. I participated in collecting the data which have been published in research in the volume which I mentioned.

Senator NELSON. You were the editor of this volume called Metabolic Effects of Gonadal Hormones and Contraceptive Steroids?

Dr. SALHANICK. Yes, that is correct.

Senator NELSON. You have then obviously reviewed the literature of the studies that have been made?

Dr. SALHANICK. We attempted to collect by various mechanisms, including chemical reviews, the various bibliography services in the world, all the literature we could find up to the time of that conference. We distributed these bibliographies to the individuals whom we thought were most expert in the various fields.

Obviously, there is wide range in that kind of selection, and they published, we think, fairly good review articles of each of seven or eight areas in that book.

In addition, we asked individuals who had been doing research currently to present their findings at that conference, and those findings are also included in the book.

Third, we encourage at that time as much discussion as possible hoping that if there were a scientific way of resolving some of our lack of knowledge that it would come out in discussion.

I can only say that after reviewing approximately 18 or 20 tapes of discussion——

Senator NELSON. Eighteen to twenty what?

Dr. SALHANICK (continuing). Tapes of discussion over a period of 4 days, that there was practically no disagreement among the scientists on the data which presented. The interpretations are another matter, but the data presented were generally accepted.

Senator NELSON. Has anybody outlined a protocol to be followed in the kind of investigations and the size and nature of them?

Dr. SALHANICK. To my knowledge, no. I think it may be very difficult to solve some of the problems which we are trying to solve. I cited some of those reasons in my statement. The various types of pills which exist mean that it is difficult to have a controlled study in respect to the type of pill.

The rapidity with which people move from one pill to another, from one city to another, means that a population for study would be difficult to locate and stabilize.

We do not know a lot about dosages. It is hard to follow patients for a long period of time and still keep in mind the primary need of the patient, which is not the research project but her particular medical problems. So that, considering all of the limitations, I think it is very difficult to do the investigation, and I think it will demand great ingenuity on the part of the investigators involved.

Senator NELSON. We have not yet had witnesses from HEW, NIH, FDA—we will have one from FDA later. Are you familiar with any research, ongoing research, by any of the Federal agencies now or any protocols they have developed for research?

Dr. SALHANICK. Yes, sir. I am on the advisory committee of the Population Center of the National Institute of Child Health and Human Development. Dr. Corfman is here, he is the head of it, and they have initiated a program to encourage investigation in the development of new contraceptives, and they have a program to attempt to define the consequences of using pills.

Protocols are developed by investigators, and it is my understanding some protocols are being investigated by the Institute itself.

Senator NELSON. How extensive have been the metabolic studies that we have had thus far?

Dr. SALHANICK. In certain respects the metabolic studies have been quite extensive in that many people have done approximately the same thing, and we come to a point where we really suffer from ignorance. The next steps are very difficult or we do not have ways of getting at it, and this is some of the current state of the knowledge, and this will require more people, more different approaches, much more work, and research unfortunately is a slow uphill endeavor in any case.

Senator NELSON. By that you mean that there have been some fairly extensive metabolic studies but you are not prepared to draw any long-term conclusions from them, is that right?

Dr. SALHANICK. Yes. Some simple things we should know we do not know. We should know, for example, more about the dose response curves. I think that is very critical information. So that regardless of what kind of course we take we would be able to use the least dose which is effective contraceptively and, to my knowledge, and I may be wrong, but to my knowledge that is not now known. So that this kind of information is necessary.

In addition, we do not have a considerable amount of epidemiological data. By that I mean we do not know the incidence of certain diseases; we do not even know how to define some of the diseases. If someone has an abnormal glucose-tolerance curve does that person have diabetes or does one have to have vascular changes to have diabetes. The terminology is very difficult in interpreting so far as whether the effects of the contraceptive steroids cause diabetes or just cause changes.

Now, until some of those items can be resolved it is hard to do a research project that says taking pills causes diabetes. We cannot do that step yet. We can only say that taking pills causes changes in the glucose-tolerance curve.

Senator NELSON. Would the studies indicate it may cause what is sometimes described as chemical diabetes?

Dr. SALHANICK. Yes, sir.

Senator NELSON. In your large volume that you edited, did the metabolic studies that were done by various individuals and groups roughly show this same thing in each of the studies?

Dr. SALHANICK. Yes. I think that is the case. I think almost everyone has found similar results. Percentages may vary, but the results are approximately the same.

Senator NELSON. Do you have any questions?

Mr. GORDON. The latest Dear Doctor letter, dated January 12, 1970, states that the sequential products are less effective and more hazardous.

Can you explain to us what the usefulness of the sequentials is since there are combinations that are more effective and less hazardous?

Dr. SALHANICK. I would have a difficult time explaining the usefulness of sequential products in the light of the combinations which are available because sequential products usually have larger doses of estrogen, and most people have the impression that the estrogen is more obnoxious than the progestational agent. In view of its decreased efficiency as a contraceptive, I really do not see that there is a great place for them.

If it were shown that the progestational agent was chiefly responsible for side effects, which we did not want to have, then the advantage of a sequential pill would be that there would be a lesser amount of the progestational agent.

In my opinion, and it is strictly my opinion, the estrogen is more responsible, is responsible for more problems than the progestational agents.

Senator McIntyre. Doctor, you point out that thus far no steroid with contraceptive action has been found to be free of metabolic effects.

As we have heard from many other witnesses, some of the metabolic side effects of the hormonal contraceptives have long-term effects on the health of the individuals to whom they are administered.

Do you think the chances are pretty good that further research will be able to produce a steroid that has contraceptive properties without metabolic side effects or do you think that the chances for such a discovery are slight?

Dr. Salhanick. I think we may find contraceptive steroids which will be effective which have minimal side effects. I do not think we will find a contraceptive which is absolutely devoid of side effects and, as we learn more about the implications of the side effects, I would become more comfortable with this area of investigation, and that is one of the reasons why I urge the investigation of other methods of contraception as well.

Senator McIntyre. You think, Doctor, that it would be a good idea to direct a larger portion of our limited research capabilities to a search for nonsteroidal contraceptives so we do not end up with all of our eggs in what may turn out to be an empty basket? [Laughter.]

Dr. Salhanick. Yes. I think we should do both, but with eight and a half million women committed to the pill, I think we have to put some tremendous efforts into that also.

Senator McIntyre. Doctor Salhanick, you indicate that the practice of equating the pharmacological state induced by the oral contraceptive with the biological state, such as pregnancy, is invalid and should be abandoned.

Some of our witnesses have made the point that, although there are serious known potential risks associated with the use of the pill, such risks are justified because the risks of pregnancy itself are greater. Do you think that this is a valid comparison?

Dr. Salhanick. No, sir, I do not; not as a generalization.

I think many women, many couples, can use alternate methods of contraception, and I think there are other alternatives to the contraceptive agents for some people.

Now, for some people there are not other alternatives, and in that case the physician involved has to make a decision of does this couple have any alternatives than to the use of the pill.

Senator McIntyre. Doctor, you point out that the amount of progesterones in some of the oral contraceptives has been reduced to about one-tenth of the minimal dose, and estrogen to about one-third without loss of contraceptive effect.

The British authorities, on the basis of studies there showing that the high-estrogen pills carry a higher risk of serious side effects, have recommended the use of the high-estrogen products be discontinued.

Since the high-estrogen pills apparently do not provide any added benefit over the low-estrogen pills in the form of increased effectiveness, do you think we would be justified in following the British example in this country?

Dr. SALHANICK. I think that with all medications once you use the lowest effective dose that will do the job, and if we have lower doses of contraceptive agents which can assure a hundred-percent efficiency, then that would be my recommendation for a contraceptive agent. In that regard, if there is excessive estrogen in some of the pills I think those pills are not desirable.

Senator MCINTYRE. I yield to the chairman.

Senator NELSON. What is the protocol for a study to determine the minimum estrogen and progesterone that ought to be in the pill?

Dr. SALHANICK. I do not know that. Those studies would have to be initiated by the pharmaceutical houses or the agencies involved or the Government. But there may be data in the files of the pharmaceutical houses which have not been published, and I just do not have that information. But, to my knowledge, in the literature no one has done a dose-response curve of the contraceptive efficiencies, and I do not know what the future plans in that respect are.

Senator NELSON. Assuming consent on the part of the user, what is the great problem about setting up a controlled study in which you would simply arbitrarily reduce the amount of the estrogens and/or progesterones in the pill down to one-tenth of what it is now?

Dr. SALHANICK. None; that is correct.

If the individuals involved experimentally are willing to participate, being fully informed, of course, that they may become pregnant at the lower dosages, then I think that is a desirable experiment.

I might add there may be alternate ways of approaching the information by having patients use mechanical methods of contraception while the study is being done, and attempting to use biological indicators for the evaluation of the dosage, so that if there were alterations in the gonadotropins, for example, which indicated that the doses were still effective as contraceptives, the subject would not be undergoing a risk of pregnancy, and the dosages would be defined to a closer approximation. The ultimate experiment, however, is the one which you cited, with some risks to the patients.

Senator NELSON. There are, of course, large numbers of users of pills who are simply using it for the purpose of spacing pregnancy, not that it is a simple matter to seek out and find these people but, on the other hand, it is not impossible, and that somebody who then was going to quit using the pill probably would be prepared to test a much lower dosage one. But you know of no such studies going on now?

Dr. SALHANICK. I am not aware of any such studies going on now; no, sir.

Senator NELSON. All right. Go ahead.

Senator MCINTYRE. I might just remark it seems like a very good suggestion in the matter of testing low-estrogen pills.

Finally, in describing the metabolic effect of the oral contraceptive, you said, and I quote:

> There appears to be a characteristic pattern whereby the metabolic reserve is challenged. When ample reserves exist the effects are less marked. But when the reserve is decreased the effects become prominent.

Could you explain to us what this means in layman's terms?

Dr. SALHANICK. Well, the problems of finding people who would be most susceptible to the metabolic effects of the agents are considerable.

Now, if one accepts this as a general principle which is generally true—namely, people who have some difficulty, say, with hypertension may be more susceptible to the pill than many others, many people who have subclinical diabetes, for example, given the pill may show up with diabetic changes. People who have had the compromises of liver function will show up with abnormalities or more abnormalities of the liver, and these are in contrast with women who are absolutely normal, and since the changes are small very often they cannot be detected in absolutely normal women. Does that answer it?

Senator MCINTYRE. Yes. Thank you very much, Doctor.

Thank you, Mr. Chairman.

Senator DOLE. Thank you, Mr. Chairman.

First of all, I wonder if you would want to elaborate on what you said on page 5. You indicate that you feel we should pursue a middle ground in some areas. For some couples, another type of contraception must be employed or should be employed if desirable. What is this intermediate course that you refer to? I am not certain I understand just what you may have in mind.

Dr. SALHANICK. Well, among all the alternatives which are presented to us are those ranging from discontinuing the use of all contraceptive pills to doing nothing. I certainly do not advocate discontinuing the use of all contraceptive pills. I think it is too important in our society at this time.

On the other hand, I think the point has been made that pills which have excessive dosages really do not have very many advantages over those of low dosages. So that this is one compromise that can be made.

I think another intermediate ground is to institute a program of investigation of not only the types which are going on now, but also those which would include surveillance of the people who have had the pills for long periods of time at high dosages, people with various kinds of abnormalities, to start with.

I think an educational program of both patients and physicians might be helpful in this. I think some patients are more sensitive to the effects than others, and I think those patients should be found and they, as a small group, could be eliminated from the usage of the pill.

So these are compromise measures as we learn more, and I think these courses should be taken.

Senator DOLE. Do you have any suggestions—there was testimony yesterday about the role of the FDA, and Dr. Goldzieher, I believe, indicated they were too rigid in their policies.

Do you have any suggestions on the proper role of the Food and Drug Administration and with reference to the very thing you suggest in your statement, more research?

Dr. SALHANICK. Well, it is difficult for me to answer the question as to the role of the FDA in research because I just do not know the structure or resources which they have for that.

I do think that they have responsibility of informing the patients and the physicians, such as has been cited in the letter which was

just mentioned, and to evaluate the drugs and, hopefully, to require the drug houses to establish proper standards.

I think that they are doing the best they can with a very difficult problem, and if we could take the data which we have one step further in terms of knowing the implications of all the findings, then one could know who was right and who was wrong in such situations. But there is an element of judgment involved, and I think their judgment has been a middle-of-the-road course insofar as their knowledge is concerned. I think now they might do some evaluations.

Senator DOLE. Yesterday, there were a series of questions propounded to Dr. Wynn, and I wonder if I might ask you to comment on two or three of these.

First, is there clinical data to suggest that the alterations in metabolism which are frequently attributed to the use of the pill are in any way related to the inevitable production of damage, permanent or otherwise?

Dr. SALHANICK. Well, I am not sure what kind of alterations you are referring to.

As I have indicated, the step between the abnormal findings and the disease is difficult to establish. Now, persons with those diseases, let us say diabetes, for example, have abnormal glucose-tolerance tests. Persons who take the pills have, to a lesser degree, abnormal glucose-tolerance tests.

Now, the next step as to whether persons with the pill have diabetes is a somewhat difficult one, and philosophical one, depending on the definitions of abnormality and definitions of diabetes, and that kind of difficulty, so I do not think that can be answered in a simple fashion.

Senator DOLE. Is it true that during pregnancy certain hormones are elevated but are biologically inactive? Would that be a true statement?

Dr. SALHANICK. Well, it is true that during pregnancy certain hormones are elevated. How one determines that a particular steroid is biologically inactive I do not know. Historically we used to think that the metabolic products of some of the steroids were inactive, and recent work has indicated that they do have biological activities which were not suspected.

Senator DOLE. Then the second part of that question which was propounded to Dr. Wynn, as I understand, you have the same results that some hormones are activated with the use of the pill. Is there any certainty that these may not be biologically inactive?

Dr. SALHANICK. I am sorry I do not understand your question.

Senator DOLE. I am not certain I do either. That is why I was asking you. [Laughter.]

Is there any link in the selection of patients from which alteration of metabolism data are derived which might prejudice the development of metabolish abnormality, such as overweight, large babies, abnormal glucose tolerance?

Dr. SALHANICK. Yes. I think this is part of what I meant by the statement, which I am beginning to think is a bad statement, the metabolic reserve. I think people who have had large babies, which is indicative of diabetes, at least the diabetic state in pregnancy, who have had previous histories of abnormal glucose tolerance tests, and so on, should be carefully considered as candidates for the pill.

The difficulty often comes in just the patients who need a hundred percent contraception most, and this is truly a very difficult problem which, I believe, physicians have to handle one by one.

Senator DOLE. Thank you. That is all.

Senator NELSON. Thank you very much, Dr. Salhanick. We appreciate very much your taking the time to make your statement.

Our next witness is Dr. Philip Corfman, Director of the Center for Population Research of the National Institute of Child Health and Human Development.

Dr. Corfman, the committee is very appreciative of your taking the time to come over here today.

Your statement will be printed in full in the record, and you may present it any way you desire, and if you wish to elaborate or extemporize on anything you have said, feel free to do so.

STATEMENT OF DR. PHILIP A. CORFMAN, DIRECTOR, CENTER FOR POPULATION RESEARCH, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT; ACCOMPANIED BY DR. DANIEL SEIGEL

Dr. CORFMAN. Thank you, Senator Nelson.

My name is Dr. Corfman. I am an obstetrician and gynecologist. I was in practice for 4 years in upstate New York before I took a research position in Columbia University. I then joined the National Institutes of Health and have been there about 5 years.

I have been Director of the Center for Population Research at the National Institute of Child Health and Human Development since the Center was established in 1968.

I have also been a member of the FDA Advisory Committee on Obstetrics and Gynecology, since 1966, and in 1968 I was appointed by Dr. Hellman to be chairman of the task force on biologic effects for the Second Report on Oral Contraceptives.

My testimony will be given in two parts. The first will be a summary of the task force report, and the second will be a description of the research on these topics underway at NIH, particularly at the National Institute of Child Health and Human Development.

I am accompanied by my colleague, Dr. Daniel Seigel. He is a statistician. He and I have been responsible for developing the studies that I shall discuss in the second part of my testimony. I would like to include Dr. Seigel in the discussion of those projects and in any questions you may direct to us.

Senator NELSON. You can handle it any way you wish. Any time Dr. Seigel wishes to make some comments he may feel free to do so. I would appreciate his comments.

Dr. CORFMAN. As far as the first portion of my testimony goes, our task force included three obstetricians, other than myself: Dr. Karlis Adamsons from Columbia University; Dr. Elsie Carrington from the Woman's Medical College; and Dr. Eleanor Delfs from Marquette University.

We met several times over a period of a year. With the help of our staffs and the National Library of Medicine, we scanned the medical literature on the subject. The initial printout by the National Library of Medicine produced a list of almost 4,000 articles of varying length and pertinence in American and foreign journals.

From this we selected about 500 articles for careful review, and included about 200 in the final report. As you can see, and as you know from previous testimony, the medical literature on this subject is extensive.

In addition, there are a number of detailed volumes on this subject, one of the most notable being a report of a conference held in Boston last December entitled "The Metabolic Effects of Gonadal Hormones and Contraceptive Steroids." This is the conference organized by Dr. Salhanick and his colleagues. You have been already directed to this.

The task force was assigned the responsibility of reviewing what is known and identifying certain topics considered to be of particular importance. The effects of oral contraceptives on blood coagulation, thromboembolism, and cancer were covered in other task force reports and people like Dr. Hertz, in particular, have been here to discuss those reports. I shall summarize our report, but for greater detail I refer you to the full report as well as other literature on this subject.

The report identified over 20 topics for discussion. I shall review a selection of these topics in the order in which they occur in the report.

One of the most important features of oral contraceptives is their effectiveness. Few, if any, pregnancies have been known to occur in the millions of women on these drugs when the drugs are used correctly. They are so effective, in part, because they have at least three contraceptive effects. The primary effect is to inhibit the hormones produced by the pituitary gland which control the reproductive cycle. A second effect changes the lining of the uterus making it inhospitable to the implantation of fertilized ova. A third effect alters the cervical mucus making it difficult for sperm to enter the uterus. This multitude of contraceptive effects is reflected in the fact that oral contraceptives have manifold effects on other body functions as well.

Our evaluation is complicated by the fact that there are many different compounds with several modes of administration and that data derived from the study of one drug may not be relevant to the effects of another. At least six variables have been identified as important: (1) the specific agent employed; (2) the absolute amount of each agent; (3) the proportion between the two agents if more than one is used; (4) the route of administration; (5) the length of time the agent is used; and (6) the age of the user. All effects are dependent on these six variables.

The task force noted that little is known about the way in which the body absorbs, handles, or excretes these agents or at least the information was not available to us from the open scientific literature. Such lack of information on the metabolism of drugs is common since research of this type is difficult and expensive, but the task force felt that such information is particularly relevant to an understanding of the biological effects of these agents.

As already noted, oral contraceptives have a profound effect on the woman's reproductive cycle. The principal contraceptive effect is inhibition of ovulation, so far as we know. The means by which this is brought about is still not clear, due in large part to the lack of uniform and satisfactory means to differentiate among the various natural hormones involved. New techniques of measuring these hormones have recently been developed and should lead to a better understanding.

Women usually begin to have normal cycles within 4 to 8 weeks after they cease medication but a few fail to institute normal menstruation for 6 months or longer. Such women become pregnant but for most women, cycles eventually resume with or without special treatment. It is not yet known if oral contraceptives actually cause this condition and it will be difficult to settle this issue since periods are known to cease spontaneously and without certain cause in about 3 percent of young women.

An important and certain effect of oral contraceptives on reproductive function is inhibition of lactation after delivery. This effect has particular importance for developing countries where children depend on breast milk for nutrition. We know that oral contraceptives in high doses will decrease or stop lactation within the first or second month of use but it appears that smaller doses have little or no significant effect, although this question has not been fully resolved.

Apparently minor changes in liver function tests have been observed in many women on oral contraceptives. The liver is one of the most complex organs in the body and has a multitude of functions, one being changing certain chemicals so that they may be eliminated from the body. A good way to test liver function and its efficiency is to measure how quickly it can help eliminate such chemicals. We know that oral contraceptives decrease the liver's ability to change one such chemical (sulfobromophathalein) in about 40 percent of women. The degree of this effect appears dependent on the amount of oral contraceptives used. It is also probably related to the fact that oral contraceptives, as well as other steroid chemicals, decrease the ability of the liver to excrete bile.

Senator NELSON. What studies have been done to evaluate the significance of the change in the liver's capacity to eliminate certain chemicals?

Dr. CORFMAN. This is the crux of the issue so far as I am concerned, Senator Nelson: to ascertain the significance of the many changes we have observed. This is why people with statistical and epidemiological skills are so important to this kind of undertaking. Many observations have been made, but we still do not know if changes in liver function indicate harm to the woman's health.

We need carefully designed epidemiological studies over a period of years to decide if these effects have any significance. The same thing applies to the changes in sugar and fat metabolism that were discussed yesterday.

Senator NELSON. Are you going to discuss at a subsequent point what studies are now underway to evaluate the significance of the effect on various organs' capacity, such as the liver?

Dr. CORFMAN. Yes, sir. I shall review our own studies in a later part of my testimony.

Another commonly observed change in liver function is an alteration in certain enzymes, chemicals normally present in small amounts which control vital body processes. An example of such alteration is the elevation in transaminase levels which occur in about 20 percent of women on medication.

Jaundice occurs in about one woman in 10,000. Such patients also show altered liver function tests. The jaundice subsides and the liver

function tests return to normal several weeks after medication is discontinued. It is thought that this effect is due to the estrogen rather than the progestogen.

One of the better known metabolic effects is the ability of oral contraceptives to modify carbohydrate metabolism. This subject is reviewed in detail for the committee by Professor Wynn and Dr. Spellacy. Recent investigations show that a significant proportion of normal women on these agents appear to handle sugar in an abnormal way. Similar alterations are often seen in pregnancy to a larger degree and the changes vary considerably according to the specific oral contraceptive used.

Oral contraceptives also appear to increase the amount of insulin which is produced as well as other agents related to the metabolism of sugar. Such effects are more pronounced with the combined rather than with the sequential regimes and less with formulations which contain no estrogen. Whereas glucose tolerance tests return to normal shortly after medication is stopped, insulin levels may remain elevated for some time.

Approximately 25 to 40 percent of women on oral contraceptives have some changes in tests of thyroid function. Not all thyroid tests are changed however. The basal metabolic rate, for instance, does not appear to be altered and there is good evidence that the true function of the thyroid is not changed.

Some tests for adrenal gland function are also changed. The levels of certain agents such as cortisol are increased and the excretion of certain normally occurring steroids is increased. There is also no evidence that these changes have an effect on health.

The effects of oral contraceptives on blood vessels are related to their known relationship with thromboembolism. It is known, for instance, that steroids alter the diameter of veins and other blood vessels. These effects are also related to the changes in blood pressure observed in some users of oral contraceptives. Several reports of hypertension have appeared and there is an increasing body of evidence that there may be a positive relationship. If this is true, the effect is mediated through a variety of factors, including effects on blood vessels and on control systems which regulate blood pressure levels.

Another biologic change of increasing concern is the effect on the way the body handles fat. This effect is closely related to changes in sugar metabolism since fat synthesis is related to insulin levels. The changes which have been observed in fat metabolism simulate levels seen in older individuals and raise concern over the possibility that these alterations may be related to heart disease. We have no knowledge, however, of the true significance of these observations.

The task force's review identified a variety of other effects, such as changes in the way the body handles water, salt, and various minerals such as calcium, magnesium, copper, and zinc. We also noted changes in lung function, and a variety of reported effects on the central nervous system. Two well-known effects on the central nervous system are depression and headache, but such information is particularly difficult to evaluate since there is great variation in these conditions and objective evaluation is hard to achieve. We also noted reports of effects on the skin and on a wide range of other body functions. These reports are clinical accounts and as yet have no statistical validity.

The last subject discussed in our report was the possible effects of oral contraceptives on babies conceived after a woman stops medication. Although there is as yet no evidence that oral contraceptives have deleterious effect in human offspring, we believe that this is a topic which deserves careful scrutiny.

I wish to conclude this portion of my testimony by reading the conclusion of our task force: "Oral contraceptives are an important and effective means of fertility regulation and family planning. For certain women they are undoubtedly the most effective method currently available. Nevertheless, it is evident that preparations now in use have a multitude of effects in many organ systems. Although it is not yet possible to draw definite conclusions about their effect on the health of women and infants, the use of these agents warrants close observation and surveillance. Effects of special concern include alterations in carbohydrate metabolism, the character and distribution of lipids, liver function, protein metabolism, and the development of hypertension as well as alterations in endocrine function."

(At this point in the proceedings the hearing was disrupted by a group of women in the audience.)

(A recess was taken.)

Senator NELSON. We will resume the hearings.

I suppose I would have to say that was the most interesting interlude we have had here for some time.

As everybody knows, all the testimony in the record is printed, and it is a public record, so that for anybody who wants to read anything that was said in any testimony in these hearings, the record will be available. The press and the other media are all here, so it is a public meeting.

Doctor, go ahead, you may proceed.

Dr. CORFMAN. The second portion of my testimony has to do with the research on this subject underway at the National Institutes of Health.

Senator MCINTYRE. What page are you on?

Dr. CORFMAN. Page 8. Incidentally, some of the questions placed by the people who interrupted our hearings were quite important.

NIH has supported research for years in fields directly and indirectly related to oral contraceptives. Several decades ago NIH research helped to lay foundations for our as yet incomplete understanding of human reproductive processes.

Senator NELSON. Just a moment, what page are you on?

Dr. CORFMAN. Page 8, first paragraph.

In the 1950's NIH scientists did some of the first work on inhibiting ovulation in experimental animals with synthetic progestogens. Dr. Hertz was one of the scientists who did this work.

The importance of such fundamental work cannot be over emphasized. This applies particularly to the issues under discussion at these hearings. Our ignorance concerning fundamental biologic processes has been identified repeatedly here and in other such inquiries. We need much more information before we can make sound judgments about the significance of the multitude of effects which have been and continue to be observed.

In 1969 NIH supported research on the medical effects of oral contraceptives at a level of approximately $1.6 million a year. Some of this research is undertaken at Institutes other than the one in which the Center for Population Research is located. For example, scientists at the National Cancer Institute are studying the relationship between the use of these agents and cancer in experimental animals. Dr. Dunn's work has already been referred to. And other work is underway at the National Heart and Lung Institute on the relation of oral contraceptives and blood clotting.

I shall now describe the work underway at the Center for Population Research.

The Center, a part of the National Institute of Child Health and Human Development, was established in August 1968, at the direction of the President. The Center is charged to undertake an organized inquiry into the population field and to be the cognizant agency for population research throughout the Federal Government. The need for population research was stated in President Nixon's message to Congress of July 18, 1969, as follows:

> * * * it is clear * * * that we need additional research on birth control methods of all types and the sociology of population growth. Utilizing its Center for Population Research the Department of Health, Education, and Welfare should take the lead in developing with other Federal agencies an expanded research effort * * *."

Our research program involves both the biological and social sciences. The biological science program is directed toward increasing the ability of couples to control the size of their families, improving the safety and efficacy of the methods used, and adding to our understanding of the genetic and biologic implications of the various forms of intervention employed. Our current emphasis is on means to limit fertility, but population research is also concerned with means to increase fertility of couples unable to have the number of children they wish.

Population research in the social sciences is much broader in scope, involving such topics as the multitude of reasons for population change, the consequences of such change, studies of population policies, and motivation for contraceptive use.

Our studies of the medical effects of oral contraceptives are an indivisible part of our total population research program. Our first population contract, written with Princeton University, was a survey of American family planning practices. This was done primarily to discover how many American women use oral contraceptives and, therefore, may be at risk, but a great deal of extremely useful sociological data was also obtained. The survey was done in September 1965 and showed that approximately 6.4 million women in the United States had used oral contraceptives at one time or another and that another 4.7 million expected to use them in the future. It is estimated that about 8 million women are using oral contraceptives now but we plan to undertake another survey this calendar year, so that a more accurate figure may be obtained.

In 1967 Congress allocated $1 million to the National Institute of Child Health and Human Development to undertake studies of the medical effects of contraceptives. This action reflected an increasing concern by the scientific community and by society as a

whole and we proceeded to negotiate several new studies. Dr. Seigel and I collaborated in this effort. The largest contract we have is with the Kaiser Foundation Research Institute in the San Francisco Bay area, in Walnut Creek.

Senator NELSON. What is that contract specifically, you said the largest in size.

Dr. CORFMAN. It costs about $1 million a year. It is now in its third year. It started at approximately $600,000 and will eventually——

Senator NELSON. And this specific study is directed at what?

Dr. CORFMAN. Its purpose is to undertake a long-term examination of a variety of medical effects. The study requires specially designed examinations in about 10,000 women each year. The examinations include the medical history, selected physical measurements, blood pressure, electrocardiogram, psychological evaluation, and a number of blood and urine determinations, each selected for its relevance to the variety of effects under study. As of this date, special facilities have been constructed and several thousand women have been examined. Data are now under analysis by a staff of research scientists and clinicians, and we expect to report findings from this study later in this calendar year.

This contract provides us a system of monitoring women and couples taking a variety of contraceptives.

This is the largest study of its kind in the United States, perhaps in the world. As far as we know only two other similar studies are underway elsewhere, both in England. These two studies and ours provide a system of surveillance to detect medical effects of contraceptives now in use and new ones which may be developed in the future.

Does that answer your question, Senator Nelson?

Senator NELSON. Yes, it does.

Dr. CORFMAN. We now support three studies designed to provide information whether oral contraceptives increase the risk of cancer. The first is conducted in family planning clinics in Los Angeles, Calif., and is designed to measure the rate at which cervical dysplasia advances toward more serious pathology in women using oral contraceptives as compared to women using other methods. Since many investigators believe that cancer of the cervix may originate as cervical dysplasia, information on progression rates from this study will have relevance to the question of whether the oral contraceptives increase the risk of cervical cancer. This study provides an early warning system to detect if there is a positive relationship.

Interesting preliminary data from this study suggests that cervical dysplasia is more common among women who choose oral contraceptives than women who choose other methods. If further analysis confirms this observation, it will mean that women who choose oral contraceptives are somehow different from women who choose other methods, even before the medication is begun.

Senator NELSON. What do you mean by that?

Dr. CORFMAN. It means there is something different about women who choose oral contraceptives. Perhaps they have different sex practices. That is the most likely explanation. This kind of information and information from other studies suggest that such women are more prone to cervical cancer before they actually start the contraceptive methods involved.

Senator NELSON. You say it will mean that women who choose oral contraceptives are somehow different from women who choose other methods, even before the medication is begun.

Are you saying that the difference in the physiological makeup of a woman who selects an oral contraceptive and not the chemicals in the oral contraceptive cause the cervical dysplasia?

Dr. CORFMAN. Partially. It looks as if there is something about women who choose oral contraceptives which make them more susceptible to this condition than women who do not choose oral contraceptives.

Dr. SEIGEL. Could I elaborate on that, Dr. Corfman?

Senator NELSON. Yes.

Dr. SEIGEL. A number of differences have been observed in oral contraceptive users and users of other methods. These include age, for example, religion, education.

Now, epidemiologists have known for some time that certain sexual practices seem to be associated with the risk of cervical cancer.

The sexual practices in women who use oral contraceptives may be different from those of women who do not. These differences may occur in frequency of intercourse, number of partners, and age at first marriage, which have all been related to the incidence of this disease. This illustrates one of the major problems in doing studies of disease in women on oral contraceptives.

Dr. CORFMAN. Our two other cancer studies have recently been approved. Their purpose is to determine if breast and uterine cancer occur with greater frequency in women using oral contraceptives than in other women. Research experience in animals makes it mandatory that this relationship in humans be carefully studied. Even if oral contraceptives do cause cancer it may not show itself for some years, as has been pointed out before to this committee.

Nevertheless, we think it is imperative to begin to monitor this condition so that we can learn as rapidly as possible whether there is any increase in the incidence of cancer in women using these drugs. It will be of equal importance to learn that no increased risk is observable.

We also have concern for thromboembolic disease of various kinds. For example, we have just initiated a study of cerebral vascular disease. Although some information is available that points to a relation between steroid contraceptive use and this condition, the number of cases studied is relatively small and many questions remain unanswered. It is particularly important to discover if some drugs are more dangerous than others. We also wish to know if we can identify the type of women who may be especially prone to this condition. The new study now underway should provide these types of information within 2 years.

Our own staff, particularly Dr. Seigel, have been active in analyzing trends of mortality from thromboembolism in the United States for women in the reproductive ages. Dr. Seigel and a colleague of his, Dr. Markush, have published a paper on this subject. The purpose was to see if the rates have shown unexpected increases since introduction of steroid contraceptives. They found no increase in arteriosclerotic heart disease or in embolism to the brain but there was a demonstrated increase in embolism to the lungs. The amount of in-

crease was roughly that observed in similar British studies. These studies and others, such as the important work of Dr. Sartwell, permit us to estimate that the number of thromboembolic deaths in the United States in 1969 due to oral contraceptives was about 240.

We also have interest in the metabolic effects of oral contraceptives. Such problems are being examined in the Kaiser-Permanente study that I mentioned. We also support the studies of Prof. Victor Wynn and his associates at St. Mary's Hospital in London. Dr. Wynn's group is one source of information on the effects of these agents on carbohydrate and lipid metabolism. Another source is the work of Dr. Spellacy, who is testifying today. His work is supported by the Food and Drug Administration. Such data have appeared in the medical literature and were discussed in considerable detail at a recent meeting at the National Institutes of Health.

One area of concern which has not yet been adequately examined is the effect of oral contraceptives on children conceived after a woman has ceased medication. Such concern is based on animal data which show that any form of medication that suspends ovulation may produce congenital anomalies. The center has negotiated a project to investigate thoroughly the effects of oral contraceptives on the woman's chromosomes. Studies of this topic are exceedingly complex and difficult, but we are developing a collaborative study involving several hospitals to examine this issue.

In summary, I wish to refer to the first four recommendations of the advisory committee on obstetrics and gynecology. Recommendations 1 and 2 refer to the need for "well-designed studies and the long-term support for studies on carcinoma of the breast and uterus and the metabolic alterations produced by the hormonal contraceptives." These problems are an important part of the research program at the Center for Population Research and we have initiated several studies. The fourth recommendation is that NIH support a national fertility survey in 1970 and, as I told you, we intend to do so.

The third recommendation, and maybe the key one, is that "substantial support be supplied to develop new methods of contraception." We agree with this recommendation. Even though oral contraceptives are undoubtedly the most effective method currently available for certain women, they are not fully satisfactory. We need others and NIH has joined other agencies in an effort to develop new ones.

Senator NELSON. If you were to recommend the studies that you think ought to be done, what would you recommend and what notion do you have as to the cost? You mentioned $1 million. If we conducted the protocols that ought to be conducted—I realize they can vary all over the lot—what do you think we ought to do?

Dr. CORFMAN. To answer what question, Senator Nelson?

Senator NELSON. Pardon?

Dr. CORFMAN. To answer what questions?

Senator NELSON. To find the answers that we ought to find to the problem of the side effects of the pill, and the research we ought to be doing on improving the pill, to get some of the answers to the questions that the witnesses day after day say that we ought to have the answers to. So just what studies ought to be done?

Dr. CORFMAN. We should have work underway on at least three levels.

First, we must bolster research on reproductive processes.

Senator NELSON. How much research is being done—when you say reproductive processes, what do you mean by that?

Dr. CORFMAN. I mean research on how the reproductive process works in humans and in experimental animals, because work in animals is so important to human experience.

Senator NELSON. All right. How much research is being done now by the Government and privately that we know of?

Dr. CORFMAN. Is your measurement money? If it is, I would say that NIH supports reproductive biology, at about $15 million this year.

Senator NELSON. On research in the field of reproductive processes?

Dr. CORFMAN. Yes. It's difficult to define the field precisely. But I would say it would be something in that order.

Senator NELSON. How much of that is in-house research, so to speak, and how much is with arrangements with private researchers or medical schools?

Dr. CORFMAN. Most of it is through grants and contracts with outside investigators. There is some work under way in NIH laboratories, but it is a relatively small proportion of the total.

Senator NELSON. At what level do you think it ought to be done, what expenditure ought to be made?

Dr. CORFMAN. It is hard to answer that precisely because so much of the work would also be related to the development of new contraceptives.

I would like to pursue the thought I was trying to develop on needed research. The second category would be clinical studies of the topics that have been brought to the attention of this committee. By this I mean studies of metabolic effects, the effect on lipids, cancer and thromboembolism, for instance. These would be clinical studies in private patients and clients of family planning clinics.

The third category of research is the kinds of studies that Dr. Seigel represents: epidemiological and statistical studies. These studies are necessary to tell us the true meaning of the clinical observations.

I believe the thromboembolism story provides a good example of what kinds of studies are needed. The story started with clinical observations, letters to the British Medical Journal, and case reports in the Swedish and American literature. These observations brought this problem to the attention of medical science, but it was not for several years, five or six at least, until well-designed, carefully controlled studies were undertaken to show that there is indeed a positive relationship between the use of the pills and oral contraceptives.

We are still in the early stage with the other problems that have been discussed, such as cancer, hypertension, and diabetes.

Senator NELSON. Dr. Salhanick mentioned the question of dose response.

Dr. CORFMAN. Yes.

Senator NELSON. Are any studies planned in that area now?

Dr. CORFMAN. I know that there has been some work done on trying to attain a dose response with the so-called minipill, with progestogens alone. If you wish, I shall be pleased to recommend people who might be able to speak on this subject.

Senator NELSON. Go ahead.

Dr. CORFMAN. I do not know if this work is being done with estrogens. I certainly agree with Dr. Salhanick that this would be something important to do.

I hasten to point out that such studies would be difficult to undertake in this country because the problem of unwanted pregnancies in women who are willing to be experimental subjects. This is one of the real problems we have in developing new contraceptives in this country.

Senator NELSON. But at the Kaiser Institute they are making studies of 10,000 women.

Dr. CORFMAN. But we are not doing dose-response studies there.

Senator NELSON. I understand.

Dr. CORFMAN. We are monitoring women who are under the ordinary care of their obstetricians in a normal clinical setting.

Senator NELSON. As I said to Dr. Salhanick, given patient-user consent by those who are spacing a pregnancy, who at some stage are going to stop taking the pill, so they can have another baby—is it not possible that there would be those who would say, well, they were willing to test a much lower dose pill as a clinical test because it is not of great significance to them whether they had another baby in 6 months or a year, that sort of thing?

Dr. CORFMAN. I think that could be done, but it would be difficult to do it this way.

Senator NELSON. Doesn't it seem that it is critically important to find out the minimum dosage of progestogen and estrogen that can be put in a pill and still be effective?

Dr. CORFMAN. I agree with you.

Senator NELSON. Has anyone, NIH or another qualified group of individuals, drafted the protocol for the type of studies that ought to be made in this whole field?

Dr. CORFMAN. Dr. Seigel and I prepared a protocol on the kind of epidemiological studies we think should be undertaken.

Senator NELSON. If the experts who have whatever knowledge there is do not prepare the proposals for research and study, how can anyone expect that the Congress would have any notion what funds ought to be appropriated?

Dr. CORFMAN. I agree. Our paper, which appeared in the Journal of the American Medical Association, described the kinds of epidemiological studies that we think should be undertaken. It also pointed out some of the very serious problems and difficulties in answering these questions.

Senator NELSON. What I am really getting at is that there are now eight and a half million women using the pill in this country, and about 10 million elsewhere in the world. It involves a very important problem, and I would hazard a guess that if proposals for appropriate protocols to do important studies were made to the Congress, the Congress would be willing, by overwhelming majority in a bipartisan way, to say this was important enough to have these studies conducted and to appropriate the money to do it.

The problem is I have no notion of what it would take, and nobody else in Congress is qualified, and we are handicapped in trying to do something about a problem that concerns everybody, without knowing what we ought to do about it.

Could we get a response from HEW or NIH for protocols and an estimate of the cost and submit it to the committee?

Dr. CORFMAN. We would welcome such a request.

Senator NELSON. Well, I am sure that everybody on this committee would like to know what it would take, I am sure I would, and perhaps we can draft a letter, if that is the right approach, and send it to the appropriate place.

I realize that you are not expected to make the decision for all of NIH. I think we may do that.

Dr. SEIGEL. I think, Senator, it should be understood we make every effort to stay alert to the clinical problems as they emerge, and to identify individuals who can do something about these problems.

Senator NELSON. I understand that. All I am saying is we would like to have your best advice, and if it is a requirement of additional moneys for research and the amounts involved are quite modest in terms of some of the things we are doing, I am sure the Congress would consider this as important a health matter as any other single one that we can think of.

Dr. CORFMAN. Splendid. We would be very happy to respond.

Senator NELSON. All right, we will.

(The subsequent information was received and follows:)

U.S. SENATE,
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C., February 2, 1970.

Hon. ROBERT H. FINCH,
Secretary of HEW, Department of Health, Education, and Welfare, Washington, D.C.

DEAR SECRETARY FINCH: This letter is in reference to our telephone conversation on Monday.

As I mentioned at that time, one thing that emerges rather clearly from the testimony on oral contraceptive drugs before our subcommittee is the urgent need for an expanded research effort, particularly in two fields:

(1) clinical and laboratory studies of women on oral contraceptives, and
(2) statistical and epidemiological studies to quantify the relationship between the use of oral contraceptives and these effects.

Dr. Philip Corfman, Director of the Center for Population Research, appeared before the Subcommittee on January 23rd and described the research on these subjects now supported by the National Institutes of Health. It would be most helpful if the N.I.H. would outline and transmit to the subcommittee a description of the additional research that they believe is necessary to conduct at this time.

I have assumed it is appropriate to direct this letter to you, rather than to N.I.H.

With best regards,

GAYLORD NELSON,
U.S. Senator.

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, March 5, 1970.

Hon. GAYLORD NELSON,
U.S. Senate,
Washington, D.C.

DEAR SENATOR NELSON: The attached report was prepared by scientists at the National Institutes of Health in response to your request of February 2 for a description of research needed to clarify issues which have been raised concerning the medical effects of oral contraceptives. The report describes research now underway in the United States and presents a plan for expansion of these programs in the next few years.

The hearings undertaken by the Monopoly Subcommittee of the Select Committee on Small Business have helped delineate many of the issues identified in this report, and we appreciate your interest in these important and difficult topics.

Sincerely,

BOB FINCH, *Secretary.*

Enclosure.

RESEARCH ON THE MEDICAL EFFECTS OF ORAL CONTRACEPTIVES

A wide variety of medical effects of oral contraceptives have been identified and have received attention in the medical and general literature. In spite of the large number of publications on these subjects, it still is not known if the changes which have been observed signify actual harm to the health of women and their children. The only exception is thromboembolism which is now thought to increase with oral contraceptive use.

A great deal of new information is required and has been delineated in two reports of the Advisory Committee on Obstetrics and Gynecology of the Food and Drug Administration, and at hearings before the Monopoly Subcommittee of the Select Committee on Small Business. The important questions which have been asked include the following: First. Do the various functional and tissue changes which have been observed signify actual harm to women, or to children conceived after discontinuing oral contraceptives? Second. What specific formulations and dose levels provide the best balance between safety and efficacy? Third. What prescribing practices do physicians employ for oral contraceptives and what aftercare is provided?

This report was prepared at the request of Senator Gaylord Nelson by scientists at the National Institutes of Health and reviewed by several experts outside NIH who are also concerned with these issues. The report begins with a review of research now supported by the Department of Health, Education, and Welfare, and by private non-profit agencies. The report notes that research on oral contraceptives is related to the broader and potentially more important field of contraceptive development, and concludes with a detailed outline of a research plan on oral contraceptives for the coming years which is consistent with the ability of the scientific community to expand investigations in these fields. The report does not examine organizational issues and is limited to the presentation of types of research underway and what is required.

DIFFICULTIES IN RESEARCH ON ORAL CONTRACEPTIVES

It is important to recognize that research on these topics is unusually difficult and that the interpretation of the data is often controversial. Indeed, there are some questions which may be impossible to answer. For instance, the constituents of oral contraceptives and their doses change with time, and it may be impossible to ascertain with certainty the effects of some of the agents now in use since in several years they may no longer be employed.

One reason research on oral contraceptives is difficult is the extended lapse of time required to answer some of the questions asked. An example is the possible relationship between oral contraceptive use and the development of cancer. It is well known that most agents proven to cause cancer in humans have a latent period of approximately ten years. For this reason, it has been necessary to wait until now to initiate studies of the possible effects of oral contraceptives on breast cancer. The initiation of such studies earlier would probably have produced negative results. Another difficulty relates to the large number of patients required to answer some questions. For example, in order to establish if oral contraceptives cause a doubling in the incidence of breast cancer, two groups of women must be followed, one on oral contraceptives and one as control, and each group must number about 25,000. Comparable studies of carcinoma of the endometrium would require 85,000 women in each group.

A third reason such studies are difficult is the simple fact that there are a large number of effects, many of which are interrelated and deal with fundamental biological processes which are often incompletely understood. The relationship between oral contraceptives and sugar metabolism is an example. It has been observed that oral contraceptives appear to alter the way the body handles sugar but the changes which have been observed are subject to different intrepretations by different experts. Indeed, there is controversy concerning the proper definition of diabetes which some have suggested may be induced by the use of oral contraceptives.

Oral contraceptives have come into wide use during a time of increasing sophistication in medical research and changing attitudes toward the use of humans as experimental subjects. It has been suggested that oral contraceptives might not be approved for general use if the decision for such use had to be made today. Factors tending toward conservatism concerning oral contraceptives are countered by the increasing recognition by scientists and society of the population problem and the right of couples to control the number of children. Oral contraceptives have become the most important contraceptive method in many parts of the country and in many family planning centers.

CURRENT RESEARCH PROGRAMS

Table 1 presents data on research underway during the most recent 12 month period for which data are available. The four categories of research are described below and titles of the individual projects are provided in Table 2. The programs of the Federal Government are presented in FY 69 since the budget for FY 70 remains in doubt. The principal agencies are the National Institutes of Health, the Food and Drug Administration, the Ford Foundation, and the Population Council. No other agencies support research in these categories to any similar extent and comparable information from the drug industry is not available.

At the present time the National Institute of Health has the largest single program, amounting to over a million dollars. The FDA supports projects at approximately $0.7 million. The programs of the Ford Foundation and the Population Council are at considerably lower levels and it is generally understood that neither of these private agencies intends to expand its programs in this area.

1. Clinic Studies

This is the largest single category of research now underway; total funds amount to approximately $1.1 million. Such research entails the intensive examinations of limited numbers of women taking oral contraceptives to elucidate the various changes which have been observed and to detect new ones. A wide variety of organ systems and functions have been shown to have been affected. These were described recently in the Second Report on Oral Contraceptives prepared for the FDA. The several changes include alterations in the reproductive tract, carbohydrate and fat metabolism, liver and protein metabolism, clotting factors, blood vessels, heart and blood pressure, lungs, central nervous system, and the fetus.

At the present time much of the research in these areas is supported on a project basis, the idea being initiated by the investigator, although a certain number of projects are initiated by the Department and supported through contracts.

2. Animal Research

Complete research on steroid hormones requires parallel studies in animals to explore certain problems which have been identified and to identify certain areas of possible risk. Animal research is now underway in a variety of species, including rodents, rabbits, dogs, and subhuman primates. Each species provides an important contribution to knowledge.

Animal work permits studies under closely controlled conditions without concern for possible risks to humans. Animal studies often require less time since the life spans of most laboratory animals are considerably shorter than the human. Furthermore, animal strains can be selected for sensitivity to certain reactions. If the drug does not cause a certain reaction in such sensitive subjects, it is more likely that the agent does not induce the effect in humans.

The current level of funding in this category is $0.4 million, much of which is used to support a single FDA study on the long-term effects of formulations now withdrawn from clinical investigation.

3. Case-Control Surveillance

Carefully designed case-control retrospective studies in humans have been used to demonstrate that there is an increased risk of thromboembolism in oral contraceptive use. This conclusion was derived from studies conducted in England and in the United States. More studies of this type are required to identify possible relationships with other illnesses, such as diabetes, cardiovascular disease, cancer, and congenital malformations. Recommendations for some such studies already approved by NIH but not yet funded are described below.

4. Specially Designed Prospective Studies

Prospective studies are needed to verify findings from the case-controlled retrospective studies and to identify which women may be subject to increased risks from serious effects. There is only one such study now underway in the United States. It is supported by the National Institutes of Health and is conducted at the Kaiser Permanente Hospital in Walnut Creek, California. This is a long-term study designed to follow women on oral contraceptives through time and to monitor the effects of these agents on their health. It provides a flexible system of surveillance and permits the study design to be changed as understanding of the problem changes. FDA is presently developing a national multi-clinic study of correlates of abnormal cervical cytology including socioeconomic status and history of contraceptive use.

RELATION TO CONTRACEPTIVE DEVELOPMENT

It is impossible to consider studies of the medical effects of oral contraceptives without also considering the closely related subject of contraceptive development. The search for new methods of contraception has received increasing attention in recent years because of their importance in helping reduce dangerously high rates of population growth throughout the world.

The Federal Government has become engaged in this search. The Center for Population Research was established at the National Institutes of Health in August 1968 to conduct research on "birth control methods of all types and the sociology of population growth" as described by President Nixon in his Population Message of 1969.

The Center's research program comprises three major areas: 1) contraceptive development and related fields of reproductive biology; 2) the medical effects of contraceptives in use; and 3) population research in the behavioral sciences. The population research budget for FY 69 was $10.8 million; the budget expected for FY 70 is $28.4 million. Most of these funds will be used for contraceptive development because of the immediate importance of this topic.

Contraceptive development and the studies of the medical effects of contraceptives in use are closely related since the latter field of investigation may lead to technological improvements in the agents or better dosage regimes. Research on oral contraceptives may also develop leads which will contribute to the development of methods based on different principles. Many scientists are dissatisfied with the contraceptives now in use, partly because of an increasing recognition of the multitude of effects produced and there is a consensus on the need for other methods which produce their effect through different mechanisms. In addition, many of the scientific procedures and systems used for studies of medical effects are also used for contraceptive development, so the coordination of these two activities is conducive to efficiencies in time and funds.

RECOMMENDED RESEARCH PLANS

A plan for research on the medical effects of oral contraceptives is described below. It requires expansion of current programs and the initiation of four new categories of studies.

EXPANSION OF CURRENT PROGRAMS

1. Clinical Studies

The studies on topics already underway should be continued and expanded. They will explore in depth the metabolic and tissue changes which have been observed and also to investigate new areas for which we have as yet no information. Department scientists and consultants should prepare a detailed research plan for the scientific community in order to generate studies in the several major scientific areas previously described. Protocols should be generated through proper notification in the scientific literature, the use of Requests for Proposals, and through individual negotiation by Departmental scientists.

2. Animal Research

Animal research now underway should also be expanded for reasons already described and it will be useful to develop a Request for Proposals similar in principle to the ones proposed for clinical studies.

3. Case-Control Surveillance

It is proposed that an organized system be established to monitor the effects of oral contraceptives in case-control retrospective studies. Such investigations will be used to determine the possible relationship between oral contraceptives and such illnesses as diabetes, cardiovascular disease, cancer, and congenital malformations. Primary sources for data will be hospitals and reporting systems already in existence. Two studies on breast cancer have been approved by NIH and await the FY 1970 appropriation. Another is being developed on the possible effect of these agents on children conceived after the interruption of oral contraceptive use. Two or three additional studies should be initiated in each of the next few years.

4. Specially Designed Prospective Studies

Research problems in oral contraceptives are similar to those encountered in studying the relation between smoking and various diseases but the problems with oral contraceptives are considerably more complicated. Both retrospective and prospective studies are often required to convince all parties concerned that a positive relationship exists; it should be pointed out that comparable difficulty may also occur in proving that a positive relationship does not exist.

One specially designed prospective study is now underway at the Kaiser Permanente Hospital in Walnut Creek, California. This important project should be expanded and one more parallel facility established, preferably one serving a different socio-economic group than does the project at Walnut Creek.

NEW STUDIES

5. Metabolism of Oral Contraceptives

There is little information on how the body actually handles the synthetic hormones in contraceptive steroids. Such ignorance is remarkable considering the widespread use of these agents. Elucidation of these processes will undoubtedly clarify the understanding of the mechanisms of action and side effects of these agents and may lead to technological improvements in steroid contraceptives.

Studies of this type will require about three years and will cost approximately $500,000 for each combination of drugs. The studies require the development of radiolabelled drugs at a cost of approximately $50,000 each and the administration of the labelled drugs to experimental subjects. These studies should then be extended to the longer term examination of the biological effect of the metabolites identified.

6. Dose Response Studies

For oral contraceptives, as for other drugs, it is important that the lowest possible dose to be used. A considerable decrease in the amount of progestogens in oral contraceptives has occurred over time but no comparable decrease in the amount of estrogens has taken place. Carefully designed studies are needed to determine the lowest possible dose which can be employed and still maintain the efficacy which has made oral contraceptives such a valuable method of fertility regulation.

To date, essentially no work of this type has been undertaken by Federal agencies or non-profit groups. Such work may have been undertaken by the drug industry but, if so, information is not available. One major difficulty with such investigation is the real risk of unwanted pregnancies in the experimental subjects.

Dose response studies are relatively short-term and inexpensive. It would cost approximately $100,000 to determine the most effective dose for any particular combination.

7. Data From Family Planning Clinics

In addition to specially designed prospective studies, oral contraceptive research should include the monitoring of data derived from family planning clinics. Such a system would be analogous to the successful Cooperative Statistical Program on intrauterine devices conducted by the Population Council. Data should be obtained on such endpoints as cervical cytology, subsequent fertility, weight gain, and depression. Some of this information is already gathered as part of routine care and more could be obtained through special design.

This data collection system could be supported through contracts or become a direct Departmental operation. The National Center for Health Statistics is now developing a nationwide record system for Federally supported family planning clinics and it is possible that the required data on oral contraceptive use could be derived from this facility.

8. *Ancillary Surveys*

A variety of surveys are required to describe the clinical and prescription practices now employed for oral contraceptives. These surveys would delineate what types of physical examinations and laboratory tests are conducted before oral contraceptives are prescribed, the frequency of physician visits, what information patients are given on potential drug hazard, the differences which may exist in diagnostic and hospitalization practice for oral contraceptive users and other women, and the ability of patients to give valid histories of contraceptive practice. Such information is of great importance to interpretation of other studies underway and have a bearing upon important decisions made by industry and government agencies concerning drug marketing.

RECOMMENDATIONS

Current research on oral contraceptives should be expanded and new studies initiated in the coming years. Such work is the responsibility of the Department. Both N.I.H. and the F.D.A. devoted $1.9 million to this field in FY 1969. The Center for Population Research at N.I.H. alone will allocate approximately $1.5 million to these studies in FY 1970 and presently expects to spend about $2.5 million in FY 1971.

TABLE 1.—CURRENT RESEARCH ON MEDICAL EFFECTS OF ORAL CONTRACEPTIVES BY AMERICAN FEDERAL AND NONPROFIT AGENCIES WITH MAJOR PROGRAMS

Category	CPR [1] (fiscal year 1969)	Other NIH [1] (fiscal year 1969)	FDA [1] (fiscal year 1969)	Ford Foundation [1] (year ending September 30, 1969)	Population council [1] (year ending December 31, 1969)	Total
Clinical studies	$148,955	$73,771	$321,206	$258,100	$284,300	$1,086,332
Animal research	44,623	70,983	245,064	10,000	65,100	435,770
Case-control surveillance	138,860	----------	176,543	----------	----------	315,403
Specially designed prospective studies	645,390	----------	----------	----------	----------	645,390
Total	977,828	144,754	742,813	268,100	349,400	2,482,895

[1] Most recent 12-month period for which data are available.

TABLE 2.—SUPPORT OF RESEARCH PROJECTS ON THE MEDICAL EFFECTS OF ORAL CONTRACEPTIVES CENTER FOR POPULATION RESEARCH, NICHD (FISCAL YEAR 1969)

Category	Project No.	Investigator, institution, project title	Annual funds
1	PH-43-67-1344	Victor Wynn, University of London, metabolic effects of oral contraceptives.	$42,704
1	PH-43-67-1389	Elizabeth Stern, University of California, Los Angeles, steroid contraception and cervical dysplasia.	106,251
2	HD-3159	Burton L. Baker, University of Michigan, hypophyseal response to estrogens and progestins.	32,283
2	HD-2537	Elizabeth Stern, University of California, Los Angeles, effects of steroid contraception in the ovary.	12,340
3	NIH-69-2250	Albert Heyman, Duke University, a collaborative study of oral contraception and cerebrovascular disease.	138,860
4	PH-43-67-1346	Frederick A. Pellegrin, Kaiser Foundation Hospitals, contraceptive drug study.	645,390
Total			977,828
		Plans for fiscal year 1970: Continuation of the above projects. In addition, the following projects have been approved but are not yet funded. Negotiations are also underway on several other projects, 1 on the possible effect of oral contraceptives on progeny (category 3):	
2	HD-4106	Mary Jane Gray, University of Vermont, effect of oral contraceptives on aldosterone secretion.	[1] 19,854
3	----------	Colin White, Yale University, a retrospective study of the risks for cancer of the breast, body of the uterus, ovary, and cervix among users of oral contraceptives.	----------
3	----------	Ralph Paffenbarger, University of California, Berkeley, oral contraceptives and tumors of the breast.	----------
5	HD-4835	Arlene P. Martin, University of Missouri, biochemical studies of 19-nor progestin metabolism.	[1] 24,208

Footnotes at end of table.

NIH (EXCEPT NICHD) (FISCAL YEAR 1969)

1	HE-2904	Helen I. Glueck, University of Cincinnati, determination of natural clotting factors with ninhydrin.	[2] $7,500
1	HE-4745	Milton G. Crane, Loma Linda University, adrenal steriod secretion rate studies.	[2] 4,500
1	HE-11046	Paul E. Slaton, Jr., University of California, San Francisco, relation of renin to volume, pressure, ions, steriods.	[2] 5,000
1 and 2	CA-8801	Jack D. McCarthy, Lovelace Foundation, contraceptive steriods and mammary cancer.	20,508
Do	HE-1275	John M. Laragh, Columbia University, electrolytes and hormones in edema and hypertension.	[2] 25,000
Do	HE-5020	Tage Astrup, James F. Mitchell Foundation, pathogenesis of arteriosclerosis.	[2] 25,000
Do	HE-9095	Michael Hume, Yale University, detection of intravascular thrombosis.	[2] 2,000
Do	HE-9852	John C. Hoak, University of Iowa, pathogenesis of hemorrhage and thrombosis.	[2] 2,300
Do	HE-11031	Milton G. Crane, Loma Linda University, effects of certain chemicals on plasma renin.	[2] 10,000
Do	HE-11591	Julian L. Ambrus, Health Research, Inc., endocrine and drug effects on thrombosis.	28,734
2	HE-12557	Ernest N. Albert, George Washington University, effect of pregnancy and oral contraceptives on uterine arteries of the guinea pig.	14,212
Total			144,754

FOOD AND DRUG ADMINISTRATION (FISCAL YEAR 1969)

Category	Investigator, institution, project title	Annual funds
1	William Spellacy, University of Miami, carbohydrate metabolism in women taking oral contraceptives.	$63,529
1	Jerome Rudolph, University of Rochester, effects of oral contraceptives on the function of the urinary tract.	77,187
1	Fritz Beller, New York University, changes in coagulation and fibrinolysis in women on oral contraceptives.	26,785
1 and 2	Russell de Alvarez, Temple University, effects of oral contraceptives on lipids in monkeys and humans.	118,127
2	Francis X. Wazeter, International Research & Development Corp., carcinogenic potential and other effects of selected oral contraceptive preparations in dogs and monkeys.	186,000
3	Philip Sartwell, Johns Hopkins University, epidemiological study of the association of thromboembolic phenomena and oral contraceptives.	176,543
4	Aaron Spector, Temple University, study of the effects of oral contraceptives on cervical cytology.	94,642
Total		742,813
	Plans for 1970: In fiscal year 1970, continuation of above projects, and initiate the following:	
1	Herbert Gershberg, New York University, differential effects of estrogen and progestin as contraceptive agents.	77,600
1	Cecil Jacobson, George Washington University, cytogenetic study of immediate postoral contraceptive abortion.	[2] 49,150
1	Thomas Frazier, Behavioral Technology Consultants, Inc., effects of oral contraceptives on behavioral energetics.	[3] 158,000

FORD FOUNDATION (YEAR ENDED SEPT. 30, 1969)

Category	Institution, project title	Annual funds
1	University of Puerto Rico, study of the long-term effects of oral contraceptives	$175,000
1	Harvard Medical School, consultation on analysis of data in a study of the long-term effects of oral contraceptives conducted by the Worcester Foundation.	6,600
1	Worcester Foundation for Experimental Biology, continuation of a study of the long-term effects of oral contraceptives.	6,700
1	University of Geneva, research in reproductive physiology	[2] 20,000
1	University of Paris, research and training in human reproduction	[2] 10,000
1	University of Delhi, research activities in reproductive biology	[2] 5,000
1	University of Chicago, an analysis of the effects of oral contraceptives	31,500
1	Women's Hospital, Mexico City, teaching and research in reproductive biology and demonstration programs in family planning.	[2] 3,300
2	University of El Salvador, research in reproductive biology	[2] 10,000
Total		268,100
	Plans for 1970: It is expected that support for the University of Puerto Rico will be terminated. The other studies will be continued.	

Footnotes at end of table.

POPULATION COUNCIL (YEAR ENDED DEC. 31, 1969)

Category	Investigator, institution, project title	Annual funds
1	Carlos Gomex Rogers, Clinica Obstetrica Universitaria, Santiago, tubal and uterine physiology and contraceptives.	$24,000
1	Herbert Kava, Albert Einstein College of Medicine, cytogenetic and genetic studies of postcontraceptive reproduction in man.	25,800
1	O. Avendano, University of Chile, administration of low dose progestins	68,000
1	George Nelson, Medical College of Georgia, heparin and oral contraceptives	15,200
1	William Spellacy, University of Miami, lipid and carbohydrate studies with megestrol acetate.	27,500
1	H. Croxatto, University Catolica de Chile, studies of effects of contraceptive steroids	58,500
1	Ruben Apelo, University of the Philippines, progestin at microdose levels	13,000
1	A. T. Gregoire, University of Michigan, biochemical investigation of cycling steroid-treated and pathological genital tract tissues.	33,000
1 and 2	Lester Salans, Dartmouth Medical School, carbohydrate metabolism and steroid contraception.	20,800
Do	Robert E Smith, Stanford University, electron microscopic studies on rabbit and human endometrium after microdose progestin.	17,800
2	Philip Dziuk, University of Illinois, Urbana, long-term administration of progestin to ewes.	13,800
2	Giuseppe Benagiano, University of Rome, biological effects of megestrol acetate	32,000
5	B. K. Adadevoh, University of Lagos, metabolism of progestational agents	30,600
Total		380,000
	Plans for 1970: Continued support at the same level.	

[1] Approved.
[2] Funds reported are part of the total grant and represent the estimated funds for studies of oral contraceptives.
[3] Required.

U.S. SENATE,
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C., March 10, 1970.

Hon. ROBERT FINCH,
Secretary, Department of Health, Education, and Welfare,
Washington, D.C.

DEAR SECRETARY FINCH: Thank you very much for the report prepared by NIH scientists on research requirements for oral contraceptives. It presents a good view of what needs to be done before we can answer important questions about the safety and efficacy of these agents and their relation to the development of new types of contraceptives.

This research is urgently needed and adequate funding and staff should be available without compromising other important health programs in the Department.

In connection with the outline of future plans as presented by NIH scientists, it would be very helpful if you would let me know the cost of the proposal program and how long it would take to complete it.

Sincerely,

GAYLORD NELSON,
Chairman, Monopoly Subcommittee.

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, May 6, 1970.

Hon. GAYLORD NELSON,
Chairman, Subcommittee on Monopoly, Select Committee on Small Business,
U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: The attached table was prepared in response to your letter of March 10 and complements our report of March 5 which outlines a plan for research on the medical effects of oral contraceptives. The table shows the funds allocated for these purposes by the Department in FY 1969 and FY 1970, and the amounts expected to be spent within the President's budget for FY 1971. The budget for subsequent years will depend on the outcome of studies now in progress, shifts in use of fertility control techniques, and the availability of funds and scientific staff. Please be assured that these research activities have my full support and will be given whatever resources we can provide within the limits of the funds appropriated for this Department.

You asked for an estimate of how long it will take to complete these studies. Some of the work, such as dose response studies, will be relatively short term, requiring only two or three years. Other studies such as the relationship between the use of oral contraceptives and cancer, of necessity require much more time. As you know, most of the proven human carcinogens require about ten years to show their effect. This is the reason that it is only now possible to undertake retrospective studies on the possible relationship between oral contraceptive use and breast cancer. Considerations of this sort make specially designed prospective studies particularly important. We expect to maintain such surveillance systems indefinitely since we shall require such systems as contraceptive technology changes with time.

Sincerely,

BOB FINCH, *Secretary.*

Enclosure.

DHEW RESEARCH ON THE MEDICAL EFFECTS OF ORAL CONTRACEPTIVES

	Fiscal year 1969				Fiscal year 1970 (estimated)				Fiscal year 1971 (President's budget)			
	CPR	Other NIH	FDA	Total, DHEW	CPR	Other NIH	FDA	Total, DHEW	CPR	Other NIH	FDA	Total, DHEW
1. Clinical studies	148,955	73,711	321,206	543,932	172,315	74,000	380,000	626,565	300,000	74,000	380,000	754,250
2. Animal research	44,623	70,983	245,064	360,670	56,480	71,000	115,250	242,730	100,000	71,000	115,250	286,250
3. Case-control surveillance	138,860	----------	176,543	315,403	247,660	----------	60,000	307,660	400,000	----------	60,000	46,000
4. Specially designed prospective studies	645,390	----------		645,390	800,000	----------	400,000	1,200,000	1,400,000	----------	400,000	1,800,000
5. Metabolism of oral contraceptives					24,208	----------		24,208	300,000	----------		300,000
6. Dose response studies									250,000	----------		250,000
7. Data from family planning clinics									250,000	----------		250,000
8. Ancillary surveys									200,000	----------		200,000
Total	977,828	144,754	742,813	1,865,395	1,300,663	145,000	955,500	2,401,163	3,200,000	145,000	955,500	4,300,500

Senator McINTYRE. Along that line, Doctor, are we in a position to come up with what the chairman is suggesting here, and what we might term a crash program? Are we in a position, do we know enough, to really hit this from all sides with a real controlled study?

Dr. CORFMAN. A crash program on the medical effects of oral contraceptives?

Senator McINTYRE. On oral contraceptives.

Dr. CORFMAN. Well, we certainly need increased work in this field. I think that the biological situation is such that some of the answers require a good deal of time. The best example is the cancer problem.

As you know from the testimony it takes a long time for proven carcinogens to cause tumors in humans. We may be a little early in launching our cancer of the breast studies, for instance, but we want to establish a baseline of information as well as pick up any changes which may have occurred by now.

Senator McINTYRE. Well, what you are saying is like an old problem I have run into many times, and that is you just cannot throw a lot of money into the problem and hope to solve it in a year or so. You indicate your studies are not in such an advanced position that you could go all out. But, of course, as you have indicated in your receptiveness to the chairman's question, you would welcome an opportunity to increase our scientific research and controlled studies on trying to come up with some answers as to whether this pill is safe or not.

Dr. CORFMAN. Yes, sir.

Senator NELSON. I think probably the most frequent observation by witnesses before the committee has been that we do not have the facts, we do not have adequate programs outlining the facts partly because of the additional question that you suggest, that some of the answers you could not get, involving cancer, for example, which is a time question. But everybody has agreed we have inadequate accumulation of statistics and inadequate programs of evaluating and seeking these statistics. We certainly think it is important enough so that it should be called to the attention of the Congress as to what would be desirable, and my guess is that you would get a very positive response.

Did you complete your statement?

Dr. CORFMAN. Yes, I did, sir.

Senator McINTYRE. Thank you, Mr. Chairman.

Dr. Corfman, in describing the various metabolic effects of the oral contraceptives surveyed by your task force you pointed out that jaundice occurs in about one woman in every 10,000 taking the pill, but that the disease subsides after discontinuation of the medication. The liver function tests return to normal several weeks after treatment is discontinued.

Now, this is an effect of the pill which we have had very little testimony about thus far. Did you find any evidence that the oral contraceptives can cause or have caused permanent liver damage?

Dr. CORFMAN. We found no significant evidence of permanent liver damage. In fact, most of the women who do become jaundiced have had some history of liver disease or of jaundice itself.

In almost every instance liver function returns to normal after medication ceases. Dr. Spellacy will speak to this in some detail.

Senator McINTYRE. You mentioned that research on the medical effects of oral contraceptives was supported by NIH at a level of approximately $1.6 million for fiscal year 1969. Could you give us the comparable figure for fiscal year 1970?

Dr. CORFMAN. For our Institute alone, the budget will be approximately $1.7 million.

The bulk of the funds that I mentioned for fiscal year 1969 are from my Institute.

Senator McINTYRE. All right.

Dr. CORFMAN. In 1969 the total NIH budget for this field was $1.7 million; $1.6 million of that was from our Institute. We expect to increase this to about $1.7 million in 1970.

Senator McINTYRE. An increase of about $100,000?

Dr. CORFMAN. Yes.

There will be another $100,000 or $200,000 of studies in other Institutes that are relevant.

Senator McINTYRE. Does that mean that the studies aimed at this pill, the comparable figure would be from $1.6 million to $1.9 million?

Dr. CORFMAN. That would be approximately correct; yes, sir.

Senator McINTYRE. I would think then that if the chairman does what he says he thinks he will, that it might be a sizable increase in the estimate or in the request for studies in response to his letter, perhaps as much as $3 million or $4 million. Is that too much money to throw at the problem on the base that you have?

Dr. CORFMAN. Certainly not; even though it takes a while to get studies underway. You have to identify the problems. You have to identify the scientists. They have to be willing to do the work. It is hard to say how rapidly you can increase a program, but we have had some experience with these kinds of increases with our contraceptive development activity. It has gone up quite rapidly.

Senator McINTYRE. Do we, Doctor, have a limited supply or not of qualified research men and facilities in this field?

Dr. CORFMAN. Of course we have a limited supply of research people and of facilities. Nevertheless, there is room for considerable expansion.

Senator McINTYRE. Would it be fair to say as a result of this response to the letter that the chairman may send that we might double our efforts?

Dr. CORFMAN. We certainly could at least double our efforts.

Senator McINTYRE. Doctor, you pointed out some of this research is being undertaken in Institutes other than the one in which your Center is located.

Dr. CORFMAN. Right.

Senator McINTYRE. As examples you mentioned research on the relationship of oral contraceptives to cancer on animals in the Cancer Institute, and work in the Heart and Lung Institute in relationship to the bloodclotting.

Dr. CORFMAN. Yes.

Senator McINTYRE. Would you tell us if any of the research being supported by either of the Institutes constitutes the kind of careful controlled prospective studies which most of our witnesses have indi-

cated are necessary in order to obtain definitive answers concerning the relationship of oral contraceptive use to cancer or thromboembolic disease in humans?

Dr. CORFMAN. No; they are not. These studies are in the second category of research that I outlined earlier. These are clinical studies of the effects of these agents in certain patient populations or in animals. The epidemiological studies have been undertaken by our Institute.

Senator MCINTYRE. Do I take that answer to mean they are not the type of controlled studies that our witnesses have said we need, and need badly?

Dr. CORFMAN. Yes, and for good reasons. The studies at the Cancer Institute are undertaken to help understand the cancer process. They are not undertaken because of concern for oral contraceptives. They are done in a different context.

Studies at the Heart Institute are undertaken to understand the blood clotting process, not to understand necessarily the effects of the oral contraceptives on women who are using them for contraceptive purposes.

Senator MCINTYRE. With respect to the work supported by your own Center, would you tell us what proportion of your funds has been devoted to research on the metabolic and other side effects of current contraceptives, including the pill, as opposed to research designed to discover a new chemical or other methods of contraception?

Dr. CORFMAN. I am pleased to give you that.

Our total population research budget for fiscal year 1970 is to be $15.6 million. This money will be used for projects, for training, for the support of population centers, and for staff support.

Of that $15.6 million, $12.9 million will go for specific research projects. Of this $12.9 million, $1.7 million is for studies on the medical effects of oral contraceptives and $9 million is for contraceptive development.

Senator MCINTYRE. $9 million for development?

Dr. CORFMAN. Yes. The remaining $2.2 million is for population research in the social sciences.

Senator MCINTYRE. Doctor, you mentioned specific studies of the metabolic effects of oral contraceptives which are being supported by your own Institute.

Which, if any, of these studies are prospective as opposed to retrospective in nature?

Dr. CORFMAN. The Kaiser Permanente study, our big one, is prospective in nature. We are following women through time and monitoring the effects of these drugs.

Professor Wynn's work is also prospective in nature.

Dr. SEIGEL. I think it would be a mistake for your committee to come to the conclusion that the only appropriate studies are prospective studies.

The justification for these other studies, those reported by the British and by Dr. Sartwell, which are called retrospective or case control studies, is that one is dealing with rare diseases like pulmonary embolism or breast cancer in young women.

If you are dealing with rare diseases of this type it is extremely difficult to bring together a sufficient number of women to study the problem and to follow them for a number of years. It is an enormously difficult administrative undertaking.

Many epidemiologists have come to the conclusion that the appropriate study for such problems is the so-called retrospective or case control study in which one gets samples of women with the condition of interest, clotting disorders, for example, and control women, and determines the contraceptive histories. This type of study has made a very valuable contribution to our understanding of the frequency of some of these rare diseases in oral contraceptive users.

Senator McINTYRE. I understand what you are saying is that retrospective studies can be of very great significance, too, in helping to solve the problem.

Dr. SEIGEL. Our basic understanding today of the thromboembolic disorders and their relationship to oral contraceptives is through such retrospective studies.

Senator McINTYRE. Thank you very much.

Dr. Corfman, do you think the first findings from the Kaiser project which you expect this year will shed any new light on the many unanswered questions concerning the effects of the oral contraceptives which have been pointed up in these hearings and elsewhere?

Dr. CORFMAN. We certainly expect that they will.

Senator McINTYRE. How long do you think it will be before we can expect suggestive if not definite results from the New York and Los Angeles studies of the relationship of oral contraceptive use to cervical cancer?

Dr. CORFMAN. The Los Angeles study is a 4-year project, and it is in its third year. We expect answers within a year.

Senator McINTYRE. Within a year.

Thank you, Mr. Chairman.

Senator NELSON. Senator Dole?

Senator DOLE. Thank you, Mr. Chairman.

Just for my own information, this may have been covered earlier in the hearing, but the unannounced questions from the floor a few moments ago by some of the ladies present did raise a question, and also in their press release, why isn't there a male pill. Will you comment on that? Is there research in this area or is it a valid question at all?

Dr. CORFMAN. Yes, I thought many of the questions the young women posed were valid and important.

We certainly have interest in male contraceptives. Other agencies interested in contraceptive development also wish to develop a modern male method. We have every reason to believe that such methods would be used. Research is underway, but I anticipate no new methods on the market for several years.

Senator DOLE. With reference to Dr. Wynn's testimony yesterday, as reported today in the press, his comments concerning an unpublished British study which demonstrates a significant increase in coronary heart disease in women under the age of 45 who have taken birth control pills, do you have any knowledge concerning this study?

Dr. CORFMAN. Nothing more, Senator Dole, than what I heard yesterday.

Senator DOLE. You are not familiar with the study?

Dr. CORFMAN. No, I am not.

Senator DOLE. You have not had a chance to review the study?

Dr. CORFMAN. No, I have not. The information is not available.

Senator DOLE. Then, secondly, as I read your testimony, I had no opportunity to read a paper that you had written in cooperation with Dr. Seigel—but have there been any studies conducted to date which would meet the standards established in your paper? Have there been sufficient numbers for any statistical certainty?

Dr. SEIGEL. I think one must be specific with respect to which end points are desired. For some of the end points like thromboembolic disorders, enough has been done so that we have some very strong suspicions about the relationships, so we can state what the relative risk is within moderate limits.

Studies have not yet been done for other end points. An example is the implication of oral contraceptive use to the outcome of pregnancy, particularly the frequency of congenital malformation. We are attempting to bring together a number of hospitals that will collaborate in a study of the health of newborn babies and the relationship, if any, with oral contraceptive use.

So I think the answer is, yes, for some end points, excellent studies have been done. For other end points, such as cancer, no one has felt that it was timely until now to do a study of the type that the British did, but studies are now getting underway.

Senator DOLE. Well, then, in view of that, and referring to the most recent report by the Advisory Committee on Obstetrics and Gynecology, a sentence that was discussed yesterday with Dr. Hellman, "when these potential hazards and the value of the drugs are balanced, the committee finds a ratio between benefits and risk within the intent of the legislation."

In other words, that would still be true despite some of the valid studies made. Dr. Seigel—do you agree with the conclusion, maybe you do not agree with the conclusion?

Dr. CORFMAN. Whether we agree with the conclusion of the committee?

Senator DOLE. Yes.

Dr. CORFMAN. I was on the committee.

Senator DOLE. I understand that.

Dr. CORFMAN. I do not feel competent to become involved with what is meant by the intent of the law but I would repeat the conclusion of our task force, which was that oral contraceptives are the most effective method currently available for certain women but they are not fully satisfactory. We need better methods.

Senator DOLE. Well, yesterday I think it was Dr. Williams who took issue with this conclusion by the committee, particularly with reference to potential hazards. I think he designated the hazards as real, and again, maybe based on your own studies, if there have been studies conducted, as Dr. Seigel says, do you think there are some large enough for some statistical certainty? The reason I raise the question whether or not they are potential hazards or they are real hazards—I am certain there are some real hazards, maybe they are not serious and maybe we do not know how serious they may be—is that I am still troubled as a layman, and I think as maybe some of these young ladies were troubled, on what they should do or what we tell them. Can you write it down on a piece of paper in a package insert; is that going to solve the problem?

Dr. CORFMAN. I am certainly in agreement with the idea that oral contraceptives are a different kind of medication. I think the former Commissioner, Dr. Ley, put it well when he said that that medication for well people should be dispensed differently from medication for people who suffer from disease.

How this is to be done I am not prepared to say except that the advantages and disadvantages of various contraceptives should be discussed in detail by the doctor and patient.

The idea of a special descriptive pamphlet for the patient is also attractive.

Senator DOLE. Do you have any comment on it, Dr. Seigel?

Dr. SEIGEL. No.

Senator DOLE. Again, in a layman's approach, and I think I am aware of some of the potential hazards, but are we able to define at this point the real hazards, the hazards that are likely to occur in using the pill? Can you enumerate one, two, three, four or is it all based on the fact that there has not been adequate study, we need more research before we can do this?

Dr. CORFMAN. The only hazard we can quantify is thromboembolism, and some people even doubt that data. It is a little like the smoking and cancer issue. Most of us feel that it is settled, but there are some who still doubt. I believe we can quantify the risk of thromboembolism but I do not think we can quantify anything else.

The other issues that have been discussed are a cause for concern, but we cannot yet say to a woman "if you take oral contraceptives you are going to increase your risk of diabetes by such and such an amount, or your risk of having cancer by such and such an amount," even if it is a zero.

Dr. SEIGEL. I had the opportunity to review some mortality statistics on thromboembolism after the British published their data, and my basic conclusion was——

Senator NELSON. Did you review the studies made by the British, the British study?

Dr. SEIGEL. Yes, sir. I have attempted to put together the mortality statistics from the United States on thromboembolism, and have published results indicating that there are increases that are consistent with the British findings.

But the point I was going to make was that I was really very reluctant to make any statement about the number of women who had died as a consequence of oral contraceptive use. That is a very sticky area. If one embarks on the exercise of determining what is the risk of death associated with oral contraceptives then one really must go through a process of asking what number of women would then become pregnant if not using the oral contraceptives, and what are the risks associated with pregnancy. There is an excellent paper on this subject by Christopher Tietze from "Studies in Family Planning" in September of 1969 which points out that for moderately effective contraception with no induced abortion, the excess risk of death would be 2.5 per 100,000 as compared to the excess risk of death with the oral contraceptive which Dr. Tietze estimated to be something like three per 100,000.

The risk associated with pregnancy is of the order of 20 deaths per 100,000 pregnancies.

Senator DOLE. Dr. Corfman, you mentioned earlier, I think, or you were present when some of the questions were raised from the floor and I am not trying to get into some of those, but if there were any of a medical nature that you might comment on it might be helpful for the record.

Were there any other questions raised that might deserve comment? You said there were a number of important questions.

Dr. CORFMAN. The only other medical one I remember was the question of the issue of abortion which was raised several times by the speakers.

Senator DOLE. Do you want to comment on that?

Dr. CORFMAN. It is certainly an important and difficult subject. We have great interest in this at NIH. We have some studies underway attempting to answer what sounds like a very simple question: How many abortions are performed in this country every year? We have no good idea about this.

Abortion is a subject of great importance to those of us interested in contraception. Moral issues aside, a good argument can be developed which shows that abortion for failed contraception decreases the need for very effective contraceptives. Perhaps one reason we are in a bind on oral contraceptives is that our laws on abortion make it necessary to use very effective contraceptive methods.

Senator DOLE. I think it was last night's news where there was a comment about some package trip from New York to England for $1,250. It included roundtrip tickets and an abortion, which again indicates or pinpoints the problem you just mentioned.

Thank you.

Mr. GORDON. This question is for Dr. Seigel. Suppose for a moment that you had a 100-percent increase in deaths as a result of taking the pill—or perhaps the lives of women are decreased by, say, 5 years.

Dr. SEIGEL. Did you say decreased?

Mr. GORDON. Decreased by 5 years.

Is there any way to detect this?

Dr. SEIGEL. You were saying a 100-percent increase in mortality for women using the pill?

Mr. GORDON. That is correct, yes; twice as many women die or a woman's life is decreased by 5 years. Is there any way to detect it?

Dr. SEIGEL. Let me answer the first question first. I think it is a little easier. There are something like 20 percent of the population, of the women in the reproductive ages, using the pill. If these 20 percent should have an increase in total mortality of 100 percent, this would have an effect upon the overall mortality on the order of 20 percent. This kind of change in mortality for women would certainly be detectable.

The kind of increment in mortality that one might expect as a result of an increase of the order of seven times for thromboembolic disorders is not easily detectable in the overall mortality because these deaths are such a small percentage of all deaths. I do not think anyone has hypothesized that it is likely that the mortality would be doubled from all causes in women on the pill, but if that were ever to take place we would certainly know it.

Senator NELSON. With the present system of reporting how would you know it occurred?

Dr. SEIGEL. Well, deaths are reported through the vital statistics systems, and you would be immediately sensitive to this in the trends in overall mortality——

Senator NELSON. Do the vital statistics that are filed indicate that a person who dies was taking the pill?

Dr. SEIGEL. No; but it would not be necessary. I think a 20-percent increase in mortality in women would be a very striking phenomena. In recent years there has been very little change in mortality in these age groups and, if anything, it has been going down.

Senator NELSON. I just wonder how you get these statistics if the death rate from thromboembolism was—I have forgotten what you said, but the incidence, I guess, is reportedly around three in 100,000 as the British say, and then out of that you upped the percentage of deaths with women taking the pill over those who do not take the pill by double, which might be 1 percent or whatever, and with the reporting system you have got, how would you know it occurred?

Dr. SEIGEL. Mr. Nelson, I think Mr. Gordon's question was with respect to mortality from all causes. Now, I would certainly agree with you that minor changes in mortality from specific causes would be very difficult to detect.

Senator NELSON. That is what I am getting at. If the death rate was, you know, one per 100,000 for a particular reason, and then in those who take the pill it became two in 100,000, we do not have any statistical compilation that would permit you to detect a difference between the one and the two, do we?

Dr. SEIGEL. It would depend on the diagnosis, and if it were a diagnostic area that is "sloppy," one in which it is easy for physicians to move back and forth between possible diagnoses. But the relative risk in the thromboembolic disorders was estimated by the British to be something like eight or nine. We have had no studies of deaths in this country from thromboembolic disorders. Dr. Sartwell's study was of cases, hospital admissions.

Now, with an increase on the order of eight times, I think it is possible to look at the statistics. One would expect an increase in mortality from those causes in U.S. mortality statistics, and indeed, there are changes in U.S. mortality from thromboembolic disorders that are consistent with the British data.

Senator NELSON. But every time the issue has been discussed here concerning the increased incidence of this disorder or that disorder, they always end up by saying, "but the statistical sample is so small that there is room for error, and we can only make sort of an educated guess."

If you had all the statistics on everybody for all causes, taking the pill or not taking the pill, I can see how statistically you can do it. I am just concerned with the fact that the reporting of these side effects and their effect on the cause of death may not be related to the pill at all.

Dr. SEIGEL. I am in full agreement with you, Senator, especially in the area of morbidity as opposed to mortality, because we do not have adequate systems of reporting hospital admissions and other types of morbidity.

We have a system, of course, which is complete for reporting mortality, the number of deaths. But that system is a very weak instrument for detecting small changes or even larger ones from some of the causes that have been studied.

Mr. DUFFY. Dr. Seigel, I suppose I should ask you this question rather than Dr. Corfman. Earlier I had asked Dr. Kistner when he made the statement that in order to have a reasonable possibility of detecting a two-fold increase in breast cancer, it would be necessary to have a prospective study involving 20,000 people.

Dr. SEIGEL. I missed the first, in order to detect the what?

Mr. DUFFY. In order to have a reasonable possibility of detecting a twofold increase in breast cancer you would require a prospective study involving 20,000 people.

I asked him at that time with reference to a reasonable possibility of detecting, does that mean there is also a possibility that you would not detect it, and he said that I had better ask you.

Now, how many people would you need in a study to assure that you would detect a twofold increase in breast cancer or any other of the side effects and complications that we speak about here?

Dr. SEIGEL. The point is discussed in a paper which Dr. Corfman and I wrote in 1968, and which was published in the Journal of the American Medical Association. We addressed ourselves to the question of what sample sizes are required to deal with some of these issues. If one were to launch a prospective study to detect a doubling of the risk of breast cancer, one would need something on the order of 85,000 person-years. This would be a minimal study. By person-years I mean you could either study one group of 85,000 women for 1 year or 10,000 women for 8 years.

But the point is that you would need enormous samples, and I do not think anyone really thinks that this is an easy way to do it.

For such diseases, the principal information has come from the opposite approach—by collecting cases of breast cancer and controls and determining contraceptive histories. This occurred in the smoking and lung cancer field where such studies were used very profitably. I think they are important here as well.

Mr. DUFFY. Mr. Chairman, do you think it would be beneficial to have that paper in the record?

Senator NELSON. Yes.

Mr. DUFFY. Would you submit that for the record?

Dr. SEIGEL. Yes.

(The document referred to follows:)

Reprinted From The Journal of The American Medical Association
March 11, 1968, Vol. 203, pp. 950-954

Epidemiological Problems Associated With Studies of the Safety of Oral Contraceptives

Daniel Seigel, SD, and Philip Corfman, MD

Most segments of American society agree that excessive and disproportionate population growth is a social, economic, and health threat, and there is a consensus, reflected in the stated policy of the federal government[1] that every family should have easy access to family planning information and services so that each may make an intelligent and uninhibited choice concerning the number of children desired. This consensus has increased the need for family planning services and efforts to develop improved techniques of contraception. New methods have been developed because the old ones are not suitable for all populations. It is difficult for a single method to satisfy all the criteria of the ideal contraceptive: efficacy, safety, reversibility, low cost, simplicity, and acceptability.

Advances in reproductive biology supported and conducted by private foundations, industry, and the government have resulted in several unique and effective techniques in the last decade, the most noteworthy being oral contraceptives and intra-uterine devices, and recent reports indicate that other promising new methods are under development.[2] The new contraceptives have proven to be acceptable in use and in many areas they are rapidly replacing more traditional methods.[3] It is estimated, for instance, that in the United States more than 4 million women are now taking oral contraceptives[4] and throughout the world, according to S. Segal, MD (oral communication, January 1967), more than 5 million women are using intra-uterine devices. This rapidly increasing use of new methods has occurred despite the warnings by some that they have not been fully tested for safety.

The literature on the effects of oral contraceptives or allied materials on biological systems is large and growing rapidly. Animal work has been conducted extensively for many years, particularly in relation to carcinogenesis, and the work relating to the constituents of oral contraceptives was discussed and summarized recently.[5] Most reports concerning the apparent effects of these medications on humans concern studies of patients with acute symptoms and are of limited significance, but the variety of presumed reactions which have been reported is remarkable in extent. Indeed, most organ systems have been implicated. Although such studies present useful indicators, few definitive conclusions can be drawn from them and it is clear that carefully designed and conducted epidemiological studies are required in order to ascertain with assurance the safety of these agents.

At present, the potential adverse effects of oral contraceptives are described in four areas.[6] The first area of concern is the potential effects on the vascular system and blood coagulation. Despite a large literature on the relationship between oral contraceptives and thromboembolism, strong evidence that such a relationship exists was not available until a recent report by the Medical Research Council of England.[7] Even so, experience is limited to retrospective studies, with little information on the pattern by which risk is increased for women with particular characteristics, such as age, parity, hemoglobin level, blood pressure, and duration of contraceptive use.

The second problem area is the possible relationship between oral contraceptives and carcinoma. It is generally agreed that a large number

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of women exposed to these drugs for many years are needed to investigate this problem, the only exception being cancer of the cervix where studies of the rates of progression from dysplasia to carcinoma in situ may be made on the assumption that such progression rates are indicators of carcinogenesis. This approach has been attempted both for study of the intra-uterine device[8] and oral contraceptives.[9]

The third set of problems is the potential development of certain metabolic diseases, such as diabetes, and the fourth is the possible relationship between oral contraceptives and the occurrence of congenital malformation in children conceived during or after cessation of medication.

The purpose of this paper is to discuss some of the difficulties that are met in studying these problems, and point out the advantages and limitations of particular approaches. Whereas the focus will be on study of the oral contraceptives, much of what will be said is relevant to the study of other methods of contraception as well.

General Problems

There are two principal approaches to the study of an association between an agent and events such as disease or adverse reactions. One is referred to as the prospective method, in which samples of persons with and without the agent are kept under surveillance for the purpose of observing the rate at which the event occurs. The other is called the retrospective or case-control method, in which individuals with the disease and appropriate controls are compared to discover the proportion of each group exposed to the agent. For example, a prospective study of the role of oral contraceptives as a carcinogen would require the observation of samples of users and nonusers for several years, and comparisons of the proportion in which cancer developed in each group. A retrospective study would require selecting a sample of cancer cases and carefully chosen controls and obtaining information from each on previous use of the medication.

Each of these methods has been used to advantage. The relationship between rubella and malformation was clearly demonstrated by a case-control study[10]; the agents contributing to an increased risk of heart disease were studied prospectively in the Framingham Heart Study.[11] In the case of cigarettes and lung cancer, both methods have been used. The early studies were largely the case-control type and suggested relationships which were later verified by prospective studies.[12]

There are circumstances that favor one or the other of these two methods that we will describe. Certain problems related to oral contraceptives beset both methods, however. For instance, the technology of oral contraceptives is constantly changing. There are two categories of drugs now available for use: the combined formulation, which is a mixture of estrogen and a progestin, taken together for 20 days with an interruption in order to permit withdrawal bleeding, and the sequential formulation, which involves the ingestion of an estrogen for the first 15 days of the cycle and a progestin for the last five days. A third formulation is now under development and shows great promise although it is not yet available for general use. It involves the ingestion of remarkably small doses of a progestin daily without interruption. Women so treated generally ovulate but, for reasons not yet understood, do not become pregnant. It is likely that this formulation may in time essentially replace the former ones.

The results of the study of one formulation may not be applicable to the others, due to the fact that effects may be dependent on dose, ingredients, and time. In addition, since formulations and schedules undoubtedly will continue to change, studies must be flexible in their design, ie, capable of adapting to a changing agent. Research programs should be thought of as systems of patient surveillance to provide early warning of possibly adverse effects.

Other problems include the changes of state that occur in persons under study. Women will interrupt use of a drug for a planned pregnancy, because of side effects, or for other reasons, and women who were not using them may start, thus altering the control group. Analysis of such checkered exposure data presents a considerable challenge. Beyond this, the use of pills is not observable. The practice of obtaining medications from family planning clinics for the purpose of selling them is well known by administrators of such clinics and epidemiologists know that respondents to interviews or questionnaires often provide responses that are designed to give a good impression, or please the physician, or avoid conflict. This is not to say that good data cannot be obtained from respondents, only that one should be concerned about the validity of responses.

The last problem common to all studies of oral contraceptives is that the investigator is usually confronted with all the biases that come with self-selection. Use of pills varies with religion, economic level, education, race, and age, to say nothing of variables of which we are unaware, and particular care is required that differences in disease rates related to these factors are not erroneously attributed to use of the oral contraceptive. Whereas one study has been initiated in which women are randomly assigned to oral contraceptives or vaginal contraceptives as controls, according to D. Rutstein, MD (oral communication, June 1967), randomization is not normally acceptable to patients. Even if attempted, the procedure is blind neither for the women nor for the examining physicians. Furthermore, where patients have preferences in the method of contraception, they may not be content with the one allocated to them, so that losses may occur at a high rate, or at differential rates from the study and control groups.

Table 1.—Minimal Samples Required to Detect Differences in Disease Rates Between OC Users and Controls in Prospective Study*

Disease	No. of Years After Onset of Study	Annual Incidence Rate in Controls per 10,000	Persons Required in Each Group: Incidence Two Times in OC Users	Persons Required in Each Group: Incidence Five Times in OC Users
Cancer of the breast	1	2.2	85,000	11,000
Cancer of the corpus uteri	1	0.3	600,000	80,000
Cancer of the cervix	1	3.1	60,000	7,500
Cancer of the breast	10	7.5	25,000	3,000
Cancer of the corpus uteri	10	1.3	140,000	20,000
Cancer of the cervix	10	5.6	35,000	5,000
Diabetes	1	20	9,000	1,200
Malformations	1	300	600	100
Thromboemboli	1	20	9,000	1,200

*OC = oral contraceptive. It is assumed that this is a simple random sample of "ever users" of ages between 20 and 45 years. Sample sizes for malformations are for births. The Table is computed for one-tailed significance tests at 0.05 level with power equal to 0.8.

Prospective Studies

Since the incidence rates of the principal problems related to the use of oral contraceptives (thromboembolic disorders, cancer, metabolic changes, and congenital malformations) are low, large populations are required to study them prospectively. In order to establish sample size requirements we must estimate (1) the incidence rate of the disease in control populations, (2) the increase in the incidence rate for groups using an oral contraceptive that is regarded as important to detect, (3) the extent to which the study should be powerful enough to detect such an increase (this power is expressed as the probability of obtaining statistically significant results, when a real difference exists), and (4) the level of the significance tests. Sample sizes increase as the incidence rates decrease, as the presumed effect of the pill decreases, as the significance levels decrease, and as the power increases. The choice of a particular set of levels for these elements depends on the social and scientific importance of the question, the prior information on the hypotheses at issue, the funds and resources available, and a number of ill-defined personality characteristics in the epidemiologic investigator.

Table 1 provides some sample sizes that are required to detect increases of two times or five times in the incidence of selected cancers, thromboembolism, diabetes, and malformation. It is assumed that the study group in each case consists of women who have ever used the drugs, that the control group is of equal size, and that both are composed of women entering a prospective study at ages between 20 to 45 years. The distribution by age in both groups is assumed to be similar to a representative sample of "ever-users," with a disproportionate number of younger women. Since the incidence rates are computed on the basis of this younger age distribution, they will be lower than would normally be seen for women aged 20 to 45. Rates are those that would be expected for the control cases in the first year of follow-up and ten years later.

For instance, a truly large sample of users, 600,000, and an equal number of controls is required to study endometrial carcinoma in the first year of observation. This hypothesis would be a reasonable one only if members of the study sample had already been exposed to medication for a substantial number of years, since carcinogens characteristically have a long latent period. The other two cancer sites require smaller samples since their incidence rates are larger.

Ten years after such a study is initiated, the ages will range from 35 to 55, and the expected incidence rates will be somewhat higher, so that smaller samples are needed. Even so, 25,000 would be required to study cancer of the breast, assuming there was a doubling in risk.

Detailed data are not available on the incidence rates for thromboembolic disorders. In a review of the epidemiology of such conditions[13] Schuman discussed the deficiency of data on morbidity and tabulated some reported studies that show a tenfold range in annual incidence of phlebitis and thrombophlebitis. The estimate of this incidence provided in Table 1, 20 per 10,000, is regarded as a rough approximation. It is similar to the experience reported by the College of General Practitioners, 2.4 per 1,000, which was observed in general practice, and consisted largely of women who were treated for superficial phlebitis of the legs.[7] Sample size requirements are considerably smaller than those for cancer, with little more than 1,000 needed where an increase in the incidence of five times is expected. Estimates of the incidence of diabetes are also difficult to obtain.[14] Judging from what is known about the prevalence and the survivorship[15] though, an incidence rate similar to that for thromboembolic disorders is likely, so that the same sample sizes are required.

The estimates for malformations pertain to births from women who have used the oral contraceptive either prior to or in some cases after the conception. Incidence rates are much greater, and sample sizes are below 1,000.

Roughly speaking, the number of persons required for these studies varies inversely with the number of years of follow-up. That is to say, two years follow-up on 1,000 persons gives approximately the same information as 2,000 persons observed for one year. The conditions under which this kind of substitution of person years for persons can be made is still being studied[16] and special care is required in the interpretation of analyses based on person-year data.

All of the sample sizes must be increased to compensate for losses to follow-up, and the increase should be roughly equal to the average number lost

each year. It should be clear that this correction will not alter biases that will result if the patients lost to follow-up have disease rates different from those who remain. Moreover, the estimates do not take into consideration interest in more specific diagnoses, such as particular malformations, more specific age groups, or particular durations of oral contraceptive usage. If answers to detailed questions of this type are sought within a single study, considerably larger samples are required.

The first of the two major problems that make prospective studies difficult is the size of the samples required. The second consists of keeping losses to follow-up at a reasonably low level, and there is no single standard of what is meant by "reasonable." One must consider such factors as the characteristics of patients lost and of those remaining, the reasons for the losses, and the degree of observed effects in the members still followed. According to C. Tietze, MD (oral communication, November 1967), in a continuing cooperative study on the efficacy and acceptance of intrauterine devices, a rate of losses to follow-up in excess of 15% in the first year at any clinic was regarded as unsatisfactory.

It would be possible to study those who have used oral contraceptives for ten years by initiating a study several years from now when a reasonable number of long-term users are available. A sample of such persons taken at that time might be more representative than the residual members of a long-term study begun now. The disadvantages of this method are that one must rely on the recall of the subjects for contraceptive experience, no base line medical measurements ordinarily are obtained, and such persons represent the remainder of a group in which many others have discontinued use of oral contraceptives for reasons that may be medically significant.

Finding appropriate populations to launch prospective studies of this type is by no means easy. Prerequisites to a significant study include a well-motivated medical staff capable of developing data and records that are of research quality; a population that is large, cooperative, and convenient to follow; and capabilities in the fine arts of data collection and analysis.

Retrospective Studies

The value of retrospective studies of disease etiology has received considerable discussion.[17-19] Criticisms of this approach take two forms. The first involves the hazards of bias in the choice of study cases or controls, and in obtaining histories. Ideally, one should be able to identify the population from which study cases are drawn, and make comparisons with controls from the same population. For hospital admissions or cases from a physician's experience, two frequent sources of study populations, it is usually difficult to identify the population that is represented. Medical facilities vary in the types of cases attracted and in the class of persons attending. Because it is difficult to identify the parent population, controls are usually selected from the same source on the assumption that they will be representative of the persons free of disease in the population from which the cases are derived, whatever that population might be. Since it usually is not possible to verify the comparability of cases and controls, multiple comparison groups are often used as a safeguard.

Table 2.—Minimal Samples Required to Detect Differences in Disease Rates Between OC Users and Controls in Retrospective Study*

Proportion of Women in Population Who Are "Ever-Users"	No. of Cases and Controls Required
0.25	120
0.50	110
0.90	340

*By proportion of women who are "ever-users" of oral contraceptives (OC). This table is appropriate for studies of cancer, diabetes, thromboemboli, and malformations. It is computed for one-tailed significance tests at 0.05 level with power equal to 0.8.

Accurate dating of disease onset and contraceptive experience is significant in avoiding bias. It is important to know if the condition existed prior to the use of medications, if medications were contraindicated, or if their use was terminated with complaints or symptoms. In addition, the quality of recall of contraceptive experience must be evaluated with care, since there may be differences in the accuracy of reporting for persons with and without disease.

The second major criticism directed at retrospective studies is that there are limitations on the kinds of information they provide. Although the investigator is interested in the risks of disease in persons using oral contraceptives, retrospective studies, by their very nature, determine the frequency of oral contraceptive use in persons with disease. Unless the investigator has information on the proportion of the population using medication and the total incidence of the disease, the risk of disease for the oral contraceptive users and nonusers will not be provided by the study. On the other hand, when the incidence of the disease is low, the ratio of risks in these two groups can be inferred[20], which is often all that is required. This was demonstrated recently in the reports relating to retrospective British studies[7] in which a trebling of the risk of thromboembolism was the central most important statistic. Furthermore, it is under this condition of low disease incidence that the case-control method shows itself to best advantage, since studies can be conducted with small sample sizes whereas prospective studies require large populations.

Table 2 presents the numbers needed for case and control samples for retrospective studies. The algebra of the computations required for this Table is such that the same results obtain for all the dis-

eases listed in Table 1, and for any others in the same low incidence range. The sample size does depend on the prevalence of oral contraceptive usage, however, and requirements are shown for three different levels of use. Numbers are given only for a doubling of the risk of disease; even smaller samples are needed if the risk is greater.

It is clear that retrospective studies require much smaller samples than prospective studies. The hazard of thromboemboli can be studied with 110 cases and 110 controls in a community where oral contraceptives are used by about half of the female population. One hundred and twenty of each would be needed if the usage were less common. This compares with samples of 9,000 for prospective studies of a doubling effect. Only for malformation is there any similarity in sample sizes indicated in Tables 1 and 2.

Just as with prospective studies, the sample sizes listed in Table 2 are minimal. An interest in subgroups, such as particular ages or types of oral contraceptives or durations of use, requires that larger groups be studied.

Summary

Much of the needed information on the longterm medical effects of oral contraceptives will be obtained only by epidemiologic studies. These studies are beset with numerous problems. Users are almost always self-selected and undergo further screening by their physicians on the basis of their medical histories. Patterns of use may be checkered with periods of discontinuance and changes in formulation prescribed. Furthermore, the drugs used, their formulations, and dose schedules are almost always subject to change.

Both prospective and case-control methods can be used for these studies and it may be advantageous to use both for certain problems. The principal difficulties with prospective studies are the large sample sizes required and biases resulting from losses to follow-up. Problems with retrospective studies include potential bias from inappropriate sample selection, difficulties in obtaining histories of illnesses and contraceptive use, and the fact that the procedure does not provide information on the incidence of disease.

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Senator NELSON. Thank you very much, gentlemen. We appreciate your taking the time. I am sorry your testimony was interrupted. It was more entertaining than your testimony, but not more effective, nor more valuable.

Our next witness is Dr. Spellacy. Dr. Spellacy is from the University of Miami Medical School.

Would you just—you did not submit any biographical data. Would you just want to briefly recite your medical background?

STATEMENT OF DR. WILLIAM N. SPELLACY, ASSOCIATE PROFESSOR, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, UNIVERSITY OF MIAMI SCHOOL OF MEDICINE

Dr. SPELLACY. Mr. Chairman, I am an associate professor in the department of obstetrics and gynecology at the University of Miami Medical School, Miami, Fla.[1]

I have been asked to review the oral contraceptives and their metabolic effects on the liver, lipids, and carbohydrates, but before reviewing these areas, let me point out the difficulties and dangers in any generalizations that I may make.

It would appear that investigation of these problems would be easy. Careful thought, however, will show that this is not true. The medical literature on the oral contraceptives is expanding at a fantastic rate. However, this does not mean that all of the experimental and clinical data can be related into a central theme. Quite the opposite. Since there are so many synthetic estrogens and progestins used in oral contraceptives, and since the dosage of each is likely to vary considerably in each commercial product, and since the duration of treatment also seems to be important as well as the characteristics of the subject taking the drug, the task of interpreting the literature is enormous. In addition, many reports do not deal with information on a pure drug-dosage-duration group, but rather upon a group of heterogenous subjects taking a variety of drugs for varying lengths of time. As a consequence, these results are virtually uninterpretable. Cross-sectional studies, where women are investigated only while taking the drugs, do not guarantee that any changes noted were not existing prior to beginning the oral contraceptives. Isolated case reports of complications may point out areas of concern to receive special study, but they do not reveal incidence figures because the size of the total treated group is unknown. Finally where animal experimental data exists, its application and relevance to humans is not always known. As a consequence, a review of this large experimental literature does not answer all of our questions, and perhaps it raises more problems than it resolves.

To find these answers will require large in-depth prospective studies of each organ system for all synthetic steroids at many dosages and drug combinations carried out for many years in a variety of different environments on many types of people. This is not practical. With this ideal in mind I will attempt then to review the existing medical knowledge in each of these three areas and to show any interrelationships and central themes that may exist.

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[1] The complete prepared statement and supplemental information submitted by Dr. Spellacy begins at p. 6439.

LIVER

As we have already heard from Dr. Corfman, the liver carries on many functions.

The anatomic structure of the liver in women taking oral contraceptives is difficult to evaluate because of the inaccessibility of the organ. Whereas, Kleiner and his associates, found normal patterns on two biopsies studied with both the light and electron microscope, three more recent reports dealing with 31 women who had liver biopsies performed while they were using oral contraceptives found changes. Although the light microscope could not demonstrate consistent changes, there were structural alterations within the liver cells involving the mitochondria particularly, which were seen with the electron microscope. Whether these alterations existed before the drugs were used, their frequency of occurrence, and whether they are progressive or reversible is not known.

The biochemical effects of the sex hormones on the liver are legion. It is well recognized for example that the liver produces most of the proteins circulating in the blood, and this production is influenced at the cellular level by ovarian hormones. Thus, giving estrogens to animals, including humans, results in an alteration in liver protein synthesis and consequently in the blood protein levels. Many of these alterations are also demonstrated by pregnant women. During either of these two conditions, estrogen treatment or pregnancy, there is a significant lowering of the total plasma protein level while the component parts show a variety of changes such as decreases in the albumin and gamma globulin and increases in other fractions. The results of these alterations are unknown. Since many clinical laboratory tests used in the diagnosis of disease states depend directly or indirectly upon the blood levels of these proteins, these tests may be "abnormal" in women taking oral contraceptives without an actual disease being present. It is important, therefore, that the practicing physicians be aware of (1) which laboratory tests are altered by the oral contraceptives and (2) which patients are taking oral contraceptives, in order that a correct diagnosis can be made.

Another important function of the liver is that of detoxification and excretion. Excretion is dependent upon the transport of blood bile salts to the liver cells and then into the bile ducts. The measurement of this excretory function can be made by injecting dyes such as Sulfobromophthalein (BSP) into the blood and measuring how fast it is removed by the liver. Kappas and his group demonstrated that estrogens interfered with this liver function and this has also been demonstrated in women taking oral contraceptives. The incidence of this abnormality varies with the dosage of the drug used. Since bilirubin is also carried from the blood to the bile in a similar manner, it is not surprising that occasionally abnormally high blood bilirubin levels are reported in women taking oral contraceptives. The effects of the oral contraceptives on an existing impaired liver function could result in the clinical manifestations of jaundice. Since pregnancy involves the same hormones, these subclinically abnormal women may also demonstrate jaundice when they are pregnant. It has been shown that approximately one-third of the women who have had jaundice while taking oral contraceptives have also had jaundice or itching while they were pregnant. It is, therefore, important that physicians

again recognize the fact that women with liver disease, or women who have jaundice or itching while they are pregnant, are very prone to develop liver complications while they are taking oral contraceptives, and this then represents a clear contraindication to their usage. Fortunately, discontinuing the drug usually rapidly "cures" the patient. Finally, it should be pointed out that no deaths have been reported from liver disease in women using oral contraceptives.

It is concluded that several of the metabolic functions of the liver are altered by the steroids of the oral contraceptives, particularly the estrogen portion. The sequelae of these alterations over long-term usage is unknown. The immediate effects include the alteration of several of the laboratory tests used in medical diagnoses. Aggravation of existing liver disease, if present, to the point where jaundice may be seen has also been shown. There is no answer to the query of will permanent liver damage result from the use of the oral contraceptives.

Next, we turn to the lipids.

The lipids or fat in the blood are divided into four major groups: (1) free fatty acids; (2) phospholipids; (3) cholesterol; and (4) triglycerides. These individual lipids are bound to plasma proteins (termed lipoproteins) and carried in the blood. That way they are transported from the site of formation to the site of use. The blood levels of each lipid depends upon a variety of factors including age, diet, weight, sex, and heredity background. In order to meaningfully study any one of these broad groups, each of the variables must be carefully controlled. The importance of the lipids in disease is principally related to the vascular system. It has been found that there is an elevation of total blood cholesterol and the low density (light) lipoprotein levels in many individuals who demonstrate clinically symptomatic coronary heart disease.

A major component of this light lipoprotein group is the triglyceride fraction. Thus, cholesterol and triglycerides are suspect to being related to the cause of this vascular disease. It is also known that there is a markedly lower incidence of coronary artery disease in premenopausal women as compared to men of the same age group or postmenopausal women. These premenopausal women have ovaries that are producing these sex hormones. It has been postulated that (1) the blood lipid levels were altered by ovarian hormones and (2) the lipid levels may be causally related to vascular disease and (3) by altering the ovarian hormone levels in the blood one could also prevent or cause serious vascular disease. Accordingly, many investigators have been conducting experiments on the effects of ovarian hormones in men and post menopausal women, since they represent the most vascular-problem prone groups. Although the results of these studies are not necessarily applicable to the young girl taking oral contraceptives, they have shown essentially no change in blood lipids with progesterone injections whereas the cholesterol and the trigycerides are lowered by estrogens.

Less information is available for the premenopausal female using the oral contraceptives. A review of these studies can be divided into the four lipid groupings. Again it should be noted that these published reports involve different drugs, different dosages, and different durations of treatment in varying types of women and accordingly, cannot always be compared or the results combined. In 1966, Dr. Wynn

and his colleagues reported that the free fatty acids were elevated in the blood of women taking oral contraceptives. More recently (1969) they have been unable to confirm this finding. Three other investigators have found normal free fatty acid levels in women taking oral contraceptives.

The second group is the phospholipids. All of the reports demonstrate an elevation of this group. This is a heterogeneous group of many subtypes of phospholipids. The medical meaning of these reported elevations that occur in women taking these oral contraceptives are not known. Recently Bolton and his associates have studied patients with arterial occlusive disease and they have found abnormal blood platelet function (important in blood clotting) which is presumably due to an elevation of the blood phospholipid lecithin. Whether the oral contraceptives elevating this particular lipid make the women susceptible to this vascular clotting is unknown.

The third lipid fraction to be considered is cholesterol. Pincus and his colleagues originally studying this group in Puerto Rico were unable to find any change in cholesterol. More recently, four research teams have found elevated cholesterol levels in their subjects using oral contraceptives. This discrepancy of results can be partially explained on the basis of the different drugs that have ben used in these investigations.

There is almost unanimity of opinion among the 10 investigating groups measuring blood triglyceride levels in women taking a variety of different oral contraceptives. All but one of the reports demonstrate a significant elevation of this lipid. Indeed Zorrilla and his group have produced similar elevations by giving women only the estrogen component of the oral contraceptive. Since these lipids are carried on blood proteins, and since we have already described the ability of estrogens to alter the liver's production of blood proteins, these lipid alterations may simply represent a difference in liver function.

Hazzard and associates have been concerned with the mechanism by which the oral contraceptive alters blood lipids. The level of blood triglycerides are dependent upon two processes: First, the production of the liver mediated by insulin and, second, the destruction at fat depots. They have investigated both processes and their results suggest that there is both an increased rate of synthesis or production of triglycerides in the liver as well as a decreased rate of enzyme destruction at fat depots in a woman taking an oral contraceptive. It is apparent that the three metabolic areas under review today (liver, lipids, and carbohydrates) are interrelated, and a primary alteration produced in one may manifest itself in the other two.

Senator NELSON. Have enough studies been made to draw any conclusions about the short- or long-term effects of these alterations?

Dr. SPELLACY. As far as the production of vascular disease is concerned, I do not think there are enough data available at this time to answer that question. It is clear that the blood levels of the lipids are changed but what effect this ultimately will have on a normal population is unknown.

Senator NELSON. And there are no studies that would indicate the effect on the user over a long period of time?

Dr. SPELLACY. Not to my knowledge. I have not reviewed Dr. Wynn's most recent data that he has related to you.

Senator NELSON. Does it raise—in your opinion—raise a serious question?

Dr. SPELLACY. Yes.

Senator NELSON. Go ahead.

Dr. SPELLACY. The medical importance of these blood lipid alterations fall into two areas. First, for the patient with an abnormal blood lipid pattern, the oral contraceptive may make her even more abnormal. I think this general theme will recur in all three of these metabolic areas, that is we are dealing with two populations, a normal and an abnormal, and it is generally the abnormal woman who becomes more abnormal soon after beginning to take these drugs and it is only a speculation as to what will happen to the perfectly normal individual with prolonged drug usage.

Zorrilla and associates have reported two women whose blood lipids were elevated before receiving an oral contraceptive and who then developed extremely high and dangerous levels of blood lipids. de Gennes and colleagues have also reported a patient who had a congenitally high blood lipid pattern and who then developed higher blood lipid levels and a stroke while receiving an oral contraceptive. It is important for the physician to know his drugs and his patients before combining them. An interesting observation has recently been reported by Glueck and associates from the NIH. They treated a group of patients with these abnormal blood lipids which were corrected by giving progestin alone. The different responses between premenopausal and postmenopausal women, between estrogens and progestins, and between normal and abnormal women, must all be considered in any study.

The second concern is for those women who are normal before receiving the oral contraceptive. This area again is only open to speculation as no definite scientific data are available to draw upon. Theoretically, if coronary artery and vascular disease is found in association with elevated blood cholesterol and triglyceride levels, then the production of higher blood cholestrol and triglyceride levels in normal women by use of an oral contraceptive may produce or predispose to vascular disease. Although several investigating groups have warned of this problem, it has not been documented to occur. A note of caution should be raised, however, in that if a requirement of time is necessary before any permanent structural alteration is manifest, for example 10 to 20 years of "hyperlipidemia" then these clinical diseases should not be seen to date.

Finally we can look at the carbohydrates. It was not until 1963 that the first suggestion appeared in the literature that carbohydrates were altered in ladies taking oral contraceptives. Since that report, there have been more than 33 published articles, dealing with carbohydrate metabolism in more than 1,633 women using the oral contraceptive for periods ranging from 19 days to more than 8 years. Although an attempt will be made to summarize these data, the same problems are encountered, that is, the reports include many different drugs, dosages, durations of treatments and types of tests and women. Nevertheless, certain information is available and some generalizations can be made.

In prospective studies where the women are tested before taking the drugs and then serially thereafter, the development of elevated blood

glucose levels is frequently seen. The incidence of this occurrence is variously reported between 0–100 percent of the time.

This discrepancy in the incidence of altered blood glucose levels seems to result from several factors, and each should be studied in some detail. First, the type of testing that is done is important and in general the more elaborate and sensitive the test that is used by the investigator, the higher will be the reported incidence of abnormal findings. Accordingly, the cortisone stimulated oral glucose tolerance test gave more abnormal results than did the plain oral glucose tolerance test or the intravenous glucose tolerance test. In general, for the group studies of short duration, the fasting blood glucose values are generally normal whereas the tolerance curve over the next 3 or 4 hours are abnormal. Second, the duration of time that the oral contraceptive had been taken seems to be important. In those studies where the duration of treatment with the oral contraceptive was several years, the incidence of abnormal results have been the highest. In one cross-sectional study of 31 women who had used the oral contraceptive continuously for more than 100 cycles, the incidence of abnormal oral glucose tolerance tests was more than 75 percent. Third, the types of subjects given the oral contraceptive is extremely important.

In a presumably normal group of women there are certain characteristics which predispose them to a statistically greater likelihood of developing an abnormal blood glucose level while using the oral contraceptives. These characteristics included: (1) women of older age, (2) those who have delivered a large number of babies, (3) those who gain excessive amounts of weight while taking the drugs or those that are obese prior to beginning the drugs; (4) those with a positive family history of diabetes mellitus; and (5) those women who had delivered infants weighing more than 9 pounds at birth.

The type of oral contraceptive also seems important. Again, it is difficult to evaluate, but several points are worth mentioning. The sequentially administered drugs have a somewhat lower incidence of abnormalities than do the combination type drugs. Admittedly the sequential preparations have been used for a shorter duration of time, and there are fewer studies performed on this group. Probably of more importance than the way the drugs are combined is the type and dosage of the steroid hormone contained in the oral contraceptive.

Senator NELSON. What do you mean by the type of steroid hormone?

Dr. SPELLACY. I will point out a little later, Senator, that the type of progestin used has a particular meaning as far as metabolic changes. There are some progestins that are virtually free of any metabolic changes, and there are some that produce very definite changes. So if a particular preparation contains a progestin that does not cause the changes that we are looking at here, then whether it is in the combined or the sequentially administered oral contraceptive, there will be fewer problems in that group of subjects.

Senator NELSON. So you are saying in the formulation of the progestin, synthetic progestin, there is a difference in the physiological consequences of the change, is that correct?

Dr. SPELLACY. Yes.

Senator NELSON. Can you identify or have those progestins been identified in their differences? Do we know what they are?

Dr. SPELLACY. Some have. They have not all been investigated, however.

Senator NELSON. And is it any problem altering the formula to create the progestin that causes this problem?

Dr. SPELLACY. No, this would seem to be one logical approach to this whole general problem. Picking out the steroids that have the fewest metabolic effects and using those in the oral contraceptives.

Senator NELSON. What studies have been done to identify this?

Dr. SPELLACY. I am only familiar with the few that are mentioned in this text dealing with particular lipids and carbohydrates. I am not familiar with other studies as for example those dealing with blood clotting or changes in cervical epithelium. I think it is a great danger in using labels such as oral contraceptives because we have such a large variety of drugs and now have it is very clearly shown, that certain of the steroids cause many more adverse changes than do the others, and to lump them all into a group under one label makes it very difficult to assess any of the existing data or to predict for the future.

Senator NELSON. Are these different steroids patented? Is it possible that some of the progestins that would cause a different kind of a problem physiologically and the one that may cause the problem in one place may cause different problems some place else?

Dr. SPELLACY. In general, when a steroid alters one area of metabolism there are alterations demonstrated in other areas. Conversely, one that is free of metabolic effect in one area is usually free in the other areas, too.

Senator NELSON. Do you know how much research is being done to identify the differences in the metabolic effects of the different groups of progestins that are being used?

Dr. SPELLACY. No, I could not give you exact figures as to the total amount of work. Perhaps Dr. Corfman could.

Senator NELSON. Dr. Corfman, does NIH have figures or studies on that problem?

Dr. CORFMAN. We could develop a list of projects, if you wish, on this subject supported by a variety of agencies. It would not be just NIH. We could do that.

Senator NELSON. There are studies identifying the difference between metabolic effects of various synthetic progestins?

Dr. CORFMAN. Well, yes.

Senator NELSON. We will go back to you then.

Go ahead.

Dr. SPELLACY. Several investigators have recently studied the estrogens and progestins separately. Although the data is still sparce, the results show that several of the estrogens alone can elevate blood glucose levels. When the progestins are investigated, there is a mixture of results with some causing elevations of blood glucose and others having little or no effect. Finally of those with an effect, it is again related to the dosage of the progestin used. For example, two studies have shown that one progestin, medroxyprogesterone, will elevate, and in contrast three other commonly used progestins (ethynodiol diacetate, progesterone, and chlormadinone acetate) show little or no change in glucose or plasma insulin. We have been investigating in a limited way some of these effects in dogs and in humans and are able to confirm most of these reports.

The dose of estrogen and the type and dose of progestin used in the oral contraceptive would certainly affect the incidence of abnormal glucose results produced in the users.

In addition to the blood glucose levels, other parameters of carbohydrate metabolism have been studied. Dr. Wynn has reviewed the studies of his own group and has noted elevated levels of blood pyruvate in 12 of 55 subjects—22 percent—studied who were taking the oral contraceptives. We first noted elevated blood insulin levels in women taking oral contraceptives and subsequently many others have confirmed this finding. Since we previously discussed the fact that insulin can increase the production of the blood lipid triglycerides, and since the levels of insulin are elevated in oral contraceptive users, we again can see how one area of metabolism being altered can affect several others. Spellacy et al. reported that levels of growth hormone in the blood are also elevated in women taking the oral contraceptive and this, too, has been confirmed.

Senator NELSON. What is the significance of increasing the level of growth hormone in the blood?

Dr. SPELLACY. We began these investigations in an attempt to elucidate the mechanisms by which the blood glucose was being changed. It is known that if one has abnormally high levels of growth hormone, as in such diseases as giantism, there is a significant elevation of blood glucose, so that this hormone can raise blood glucose levels. It has also been shown that estrogen can raise the levels of this hormone. If the estrogen is given to men or postmenopausal women or premenopausal women, their levels of growth hormone accordingly goes up. Whether or not this elevated level that we measure in women taking estrogen is biologically active or whether it is inactive is not known.

The remaining questions are two in number: first, are these changes reversible, and, two, are they harmful?

There are no complete studies available as to the reversibility of these changes. In short-term investigations of only 1 to 4 months duration of treatment, the changes are usually reversible. For the longer duration studies, the data is meager. This is because of several factors. The subjects discontinue from the studies for a variety of reasons and they can therefore not be located for followup testing, or they refuse to discontinue the drugs so that the reversibility of the alterations can be tested.

Probably the most significant question concerns itself with the possible medical hazards resulting from these alterations in carbohydrate metabolism. This question should be looked at in two parts. First, the patient who has a slightly abnormal carbohydrate metabolism when not taking oral contraceptives may be converted from a latent disease to overt, insulin requiring diabetes mellitus if given these drugs. There is little controversy about giving the overt diabetic patient the oral contraceptive. The control of her disease may be slightly more difficult with the oral contraceptive, but it can be handled medically.

The final problem concerns the normal subject who is given the oral contraceptive. One clinicial finding which may be encountered is the development of a vaginal yeast infection—candida albicans. This

problem is significantly more common in oral contraceptive users, but it can be medically handled and although a nuisance, it is not a serious health hazard.

The production of diabetes mellitus would be a health hazard. No reliable information is available on this question at this time. Wynn and Doar noted that 13 percent of their subjects developed a chemical diabetes while taking the oral contraceptive and have warned of this complication as have others. There is no confirmed data at this point. Since again we are discussing a theoretical disease occurrence which probably requires many years to develop, there is no answer now. An awareness of the problem, persistence of observation, and close followup of the treated patients is obviously necessary.

In conclusion, the data that I have reviewed for you today lends itself, I think, into two general areas. First, in the scientific area there are several important points that can be made. It should be immediately striking that the conclusions we are drawing come from very small sample sizes. For example, more than 18 million women are presumably using these drugs whereas the liver biopsy reports and the long-term carbohydrate studies are based upon 31 women each. Most of the metabolic processes seem to be interrelated as with the liver-lipids-and carbohydrates. A primary alteration in one may lead to significant alterations in the others. These alterations have to be considered for two types of populations. The one group are those with an already latent disease status, such as the women with a history of jaundice of pregnancy, abnormally high blood lipids or high levels of blood glucose. This group, although small in number, is particularly prone to develop serious medical complications from the use of oral contraceptive. The prescribing physicians must be made aware of these facts and they must recognize these women so that they can be given some other form of conception control. The larger population will be presumably normal and for them the potential production of serious complications such as liver disease, vascular disease, or diabetes mellitus are only a theoretical speculation at this time.

For the philosophical area of conclusions there are significant lessons to be learned from the past. As new modalities of conception control are introduced into medicine for normal subjects, it is important that ongoing prospective in-depth studies of their toxicity be carried out. In December 1969 Dr. Edward Tyler and others of Los Angeles published their long-term followup of one of the first groups of women in the United States to be given the oral contraceptives. Now after 12 years of use and with a current population of more than 8 million women taking these drugs in this country, they can report on but 176 women using the same drug, but at varying dosages, for only 4 to 10 years. The maintenance of a large core group for followup is not easy nor inexpensive, but it must be done to insure the safety of future generations. The studies must follow a pure research design utilizing selected drugs and isolated component steroids at the minimum dosages needed for effectiveness, then in future reviews we will no longer need to refer to "oral contraceptive studies" but to specifics such as the progestin x study of 17 women taking the drug for 36 months' time. Only this kind of information will be particularly meaningful.

Practicing physicians must be kept aware of the recent advances in our knowledge of fertility control so that their patients receive the

most effective and safest form of treatment possible. And finally, newer methods of conception control should be developed. The fact that in these studies just related to you, the estrogen component of the oral contraceptive can be implicated in most of the adverse reactions suggests that the "mini-pill" era of conception control utilizing certain progestins alone may be at least a temporary solution to our problems. Continued scientific investigations and communications are imperative.

Senator NELSON. Your field is obstetrics and gynecology. Are you in a teaching hospital?

Dr. SPELLACY. That is correct, it is the University of Miami.

Senator NELSON. Do you have a private practice?

Dr. SPELLACY. Yes.

Senator NELSON. Several witnesses have expressed their view about the duration of the period that the pill ought to be prescribed, the variation being that Dr. Kistner did not see any grave dangers through an extended period of use, whereas Dr. Hugh Davis of Johns Hopkins, if it were to be used, I hope I am stating him correctly, should be limited to use for spacing pregnancies over maybe a 2- or 3-year period. Some others have been—Dr. Hertz, I think, was somewhat more reserved respecting time and purpose of use.

Do you have a viewpoint to express on that?

Dr. SPELLACY. Yes, I think that if one is using these drugs over a long duration of time that the subjects being treated should be closely monitored. Some blood studies should be performed as well as Paps smears and a routine physical examination.

I believe that we do not have enough information available at this time to establish a time limit for the continuous use of these drugs such as 6 months or 2 years or what have you.

We also cannot put our heads in the sand and ignore the existing data however, and as physicians we must recognize that there are potential problems, and each subject must be monitored as closely as possible while taking these drugs during the long-term treatment. I think the experimental literature that is available on cross-sectional studies of ladies who have taken these for a long time do show more and more adverse reactions with increased duration of use.

The unfortunate thing in all of these studies is that we do not know what the population was like prior to their starting the drug. We cannot really say that they were all perfectly normal 5 or 10 years ago, and to get these final answers is going to require that a "core study group" be carried from now on.

Senator NELSON. All the witnesses who commented on it insisted that regular medical examinations were necessary with the variation in time being from once a year to once every 6 months to then once every 3 months, some saying that, I suppose, a general physical, plus a Paps smear, plus a breast examination, and Dr. Laragh said that blood pressure should be taken every 2 or 3 months.

Do you have any view on what the nature of the physical ought to be and the frequency, and the procedures that ought to be followed?

Dr. SPELLACY. Yes, I do.

It is clear for all of these parameters studied that we are dealing with two types of populations. Ideally the clinician should preselect out the abnormal subjects and use another form of contraception for

them. Unfortunately, these women cannot all be recognized by the tests and exams that we use today. In other words, some of the diseases are so latent that unless one does extremely extensive testing, they are not recognizable. What the doctor can do, however, is notice that this group becomes overtly abnormal very quickly, so for example that the patient with underlying vascular disease develops here hypertension very soon after starting on the pill. Therefore I believe that the first visit after beginning the drug has to be relatively soon so that this group that is abnormal is recognized and the drug stopped. I would recommend that this exam be at 3 months after starting the drug. Then after that, we are dealing with a very low yield of abnormal things occurring, and we could place the next repeat visits somewhere out between 6 and 12 months.

Senator NELSON. Several witnesses over the period of the hearings had commented in one way or another about the question of how many people do go through the examination, and cannot get very firm figures on that with the estimates being that in good clinics, the examination is done regularly and good procedure is followed. In other parts of the country probably not. It appears, although we have not taken testimony on it, but from conversations with a couple of pharmacists, they occasionally get a prescription which is renewable upon request. That was a problem also mentioned in testimony here about people who are in countries where there is no availability of physicians to do the examining.

What kind of an issue are we raising when in this country, where we either are not informed that we must have an examination or cannot afford it that regularly, and other countries where there is no medical facility available and they are taking the pill?

Dr. SPELLACY. In this country, we have a physician manpower problem. However, I believe there are enough physicians to do this type of examination. One of the problems is keeping physicians informed of the tremendous expanding literature on this particular subject. This is one area that a central organization with expertise in the scientific interpretation of this expanding literature could be helpful by periodically sending to all physicians reviews in succinct form describing the pertinent complications, the tests to be performed, and the intervals that these tests should be repeated in the subjects taking these drugs.

Senator NELSON. Where should that responsibility lie?

Dr. SPELLACY. I am not in a position to say where that should lie, but probably some Federal organization such as FDA. This should be current information sent not every 5 years, but perhaps once a year.

Senator NELSON. Dr. Wynn testified yesterday that because of the great prestige of the pharmaceutical industry and the medical profession and the fact that we have a highly regarded regulatory agency, the FDA, that all over the world, South American, for example, they simply rely upon the fact that if it is manufactured in this country and distributed in this country that it is safe, and he said the pill is being widely used in these other countries without adequate supervision.

Dr. SPELLACY. We certainly have responsibility to monitor this in our own country and also to disseminate the information to the world as it appears.

I believe that relying solely on the pharmaceutical industry to inform the physicians of these things is shedding our responsibility as a medical group to keep ourselves informed.

Senator NELSON. But what about the problem of it being widely used in other countries where, in fact, even if the user wanted to have a physical exam and understood it was necessary, facilities are not available? Perhaps every doctor in this country would say that you must have a physical exam; sound medical practice requires it to protect the user. But yet it is being used all over the world where there are no medical facilities under circumstances which any doctor in this country would say, "I will not permit my patient to have it if they are not going to take the exam."

Dr. SPELLACY. We should strive for the ideal practice of medicine by doing these regular examinations and in certain select groups very detailed in-depth research studies on these drugs. This cannot be done for all 18 million ladies but it can be done in selected countries and in select groups. With this information we can recognize these complications earlier and direct our efforts toward new means of conception control, be it different steroids or different combinations of steroids or completely different modalities, we can then introduce these safer methods into the world population control centers.

Senator NELSON. But it is being introduced now, some 10 million, 12 million women, many of whom do not live in developed, highly sophisticated societies such as the Scandinavian and the British, the German and the French, but do live in South America and do live in India, and do live in all kinds of countries without a sophisticated medical profession, and there is no answer to that question. It seems to me to raise a serious question that a device which we say medically in this country requires a physical examination, is sent to a place where a physical examination simply is not available because they do not have personnel.

Dr. SPELLACY. But it becomes a choice of the lesser of evils for that particular population in say South America. The risks, though minimal, from taking the drug without medical supervision are probably considerably less than those of not taking the drug at all. Again the United States should seek the ideal, establish the standards, protect our women, and help others to follow our methods.

Senator NELSON. It might be a decision they ought to make for themselves, and I am afraid they are.

Well, are there any other questions?

Senator DOLE. Just briefly.

I think you raise a dilemma at page 5 and page 9. On page 9 you state that an immediately striking conclusion we are drawing comes from very small sample sizes. On page 5 you make reference to a study in 1966 by Dr. Wynn and Dr. Doar reported an elevation of free fatty acids in the blood of women taking oral contraceptives, and then in 1969 they were unable to confirm this finding. I assume what you are saying to us, in effect, in many areas we are just dealing with uncertainty because there has not been an adequate sampling, there is no statistical certainty. You pointed out the study in Los Angeles involving 176. There are some 18 million, I assume worldwide, who are using the pill, and you point up that it is very difficult and also expensive to have a controlled group.

What do you suggest that we may do to make certain that we find a better pill or a safer pill or some other contraceptive because of difficulties you recite?

Dr. SPELLACY. There are metabolic changes that are still in debate. There are also areas of change that are very clear. For example, elevations of triglycerides, glucose, and insulin. These occur for most of the drugs in any population, studied in most laboratories, so you do not have to do a hundred thousand ladies to document this statistically.

What can we do to avoid this? Well, in Dr. Corfman's section they are pursuing other means of conception control, and this is certainly one approach but probably with a distant solution. We have an immediate problem and we do not want to wait for another 30 years for a solution so let us hope in the next 3 or 5 years we can switch these women to an intermediate drug as a preparatory solution. Research and development must be continued. Thus there may be three phases: (1) monitor our women on the current oral contraceptives, (2) develop a less toxic form of conception control as an intermediate solution, and (3) continue basic research for a new means of nondrug conception control.

Senator DOLE. What do we do in the meantime, do we continue to use the pill?

Dr. SPELLACY. This would be my phase 2 intermediate solution. We should abandon the use of the term "oral contraceptive." We should find the steroid(s) that will prevent pregnancy and that has the least amount of adverse effects. Although we do not know what happens if you walk this earth for 20 years with a high blood triglyceride levels, but it makes some of us uneasy. There are steroids that can prevent pregnancy and which allow women to walk this earth without high blood triglyceride levels. It would seem to me that the approach in the interim until better methods are available, would be to move in the direction of the use of safer steroids.

Senator DOLE. That is all I have.

Mr. GORDON. Doctor, someplace in your statement, I do not recall what page, you refer to a drug, chlormadinone.

Dr. SPELLACY. Yes.

Mr. GORDON. What kind of a drug is that?

Dr. SPELLACY. That is one of the many progestins, it is a synthetic progesterone-like drug.

Mr. GORDON. Is this connected with the minipill that was withdrawn from——

Dr. SPELLACY. It has been studied as a minipill.

Mr. GORDON. And is this a dangerous drug?

Dr. SPELLACY. Apparently if you are a beagle dog, female. The studies that we and others have performed in humans show very few effects of this steroid on metabolism as compared to, for example, estrogen or some of the other progestins.

Mr. GORDON. Is this now in any of the pills that are on the market?

Dr. SPELLACY. Yes; it is one of the sequential oral contraceptives which have been studied extensively, and I think this is probably a partial explanation for the fact that "sequentials" get branded as not having much effect on carbohydrate metabolism; that is, the ones studied contain that specific progestin. Again we come back to the importance of specifying what kind of progestin is involved in the oral contraceptive under study.

Mr. GORDON. But this is conducive to cancer in beagles, is that it?

Dr. SPELLACY. I have not read that report. Beagles spontaneously can develop cancer of the breast.

Senator NELSON. Thank you very much, Doctor. We appreciate your testimony. It has been very useful to us as that of Dr. Corfman, too, and we appreciate your patience.

(The complete prepared statement and supplemental information submmitted by Dr. Spellacy follows:)

STATEMENT OF WILLIAM N. SPELLACY, M.D., ASSOCIATE PROFESSOR, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, UNIVERSITY OF MIAMI SCHOOL OF MEDICINE

EFFECTS OF THE ORAL CONTRACEPTIVES ON THE LIVER, LIPIDS, AND CARBOHYDRATES

I have been asked by this committee to review for them the effects of the oral contraceptives upon three aspects of metabolism; the liver, lipids, and carbohydrates. It is an honor and a privilege for me to come here and attempt to do this.

Before reviewing these three areas, let me point out the difficulties and dangers of such generalizations. It would appear that investigations of these problems would be easy. Careful thought, however, will show that this is not true. The medical literature on the oral contraceptives is expanding at a fantastic rate. However, this does not mean that all of the experimental and clinical data can be related into a central theme. Quite the opposite. Since there are so many synthetic estrogens and progestins used in oral contraceptives, and since the dosage of each is likely to vary considerably in each commercial product, and since the duration of treatment also seems to be important as well as the characteristics of the subject taking the drugs, the task of interpreting the literature is enormous. In addition, many reports do not deal with information on a pure drug-dosage-duration group, but rather upon a group of heterogenous subjects taking a variety of drugs for varying lengths of time. As a consequence, these results are virtually uninterpretable.

Cross-sectional studies, where women are investigated only while taking the drugs, do not guarantee that any changes noted were not existing prior to beginning the oral contraceptives. Isolated case reports of complications may point out areas of concern to receive special study, but they do not reveal incidence figures because the size of the total treated group is unknown. Finally where animal experimental data exists, its application and relevance to humans is not always known. As a consequence, a review of this large experimental literature does not answer all of our questions, and perhaps it raises more problems than it resolves. To find these answers will require large in-depth prospective studies of each organ system for all synthetic steroids at many dosages and drug combinations carried out for any years in a variety of different environments on many types of people. This is not practical. With this ideal in mind I will attempt then to review the existing medical knowledge in each of these three areas and to show any interrelationships and central themes that may exist.

A. Liver

The liver carries on many functions within the body.

The anatomic structure of the liver in women taking oral contraceptives is difficult to evaluate because of the inaccessability of the organ. Whereas Kleiner and associates found normal patterns on two biopsies studied with the light and electron microscope (1), three more recent reports dealing with thirty-one women who had liver biopsies performed while they were using oral contraceptives found changes. Although the light microscope could not demonstrate consistent changes, there were structural alterations within the liver cells involving the mitochondria particularly, which were seen with the electron microscope (2–4). Whether these alterations existed before the drugs were used, their frequency of occurrence, and whether they are progressive or reversible is not known.

The biochemical effects of the sex hormones on the liver are legion. It is well recognized for example that the liver produces most of the plasma proteins, and that this production is influenced at the cellular level by these hormones. Thus, giving estrogens to animals, including humans, results in an alteration in liver

NOTE.—Numbered references at end of statement.

protein synthesis and consequently in the blood protein levels. Many of these alterations are also demonstrated by pregnant women. During either of these two conditions, estrogen treatment or pregnancy, there is a significant lowering of the total plasma protein level while the component parts show a variety of changes such as decreases in the albumin and gamma globulin levels and elevations of fibrogen, ceruloplasma, plasminogen, transcortin and the thyroid binding globulins (5). The results of these alterations are unknown. Since many clinical laboratory tests used in the diagnosis of disease states depend directly or indirectly upon the blood levels of these proteins, these tests may be "abnormal" in women taking oral contraceptives without an actual disease being present. It is important, therefore, that physicians be aware of (1) which laboratory tests are altered by the oral contraceptives and (2) which patients are taking oral contraceptives, in order that a correct diagnosis can be made.

Another important function of the liver is that of detoxification and excretion. Excretion is dependent upon the transport of blood bile salts to the liver cells and then into the bile ducs. The measurement of this excretory function can be made by injecting dyes such as Sulfobromophthalein (BSP) into the blood and measuring how fast it is removed by the liver. Mueller and Kappas demonstrated that estrogens interefered with this liver function (6) and this has also been demonstrated in women taking oral contraceptives (1, 7). The incidence of this abnormally varies with the dosage of the drug used (8, 9). Since bilirubin is also carried from the blood to the bile in a similar manner, it is not surprising that occasionally abnormally high blood bilirubin levels are reported in women taking oral contraceptives (9, 10). The effects of the oral contraceptives on an existing impaired liver function could result in the clinical manifestations of jaundice. Since pregnancy involves the same hormones, these subclinically abnormal women may also demonstrate jaundice when they are pregnant. Ockner and Davidson reviewed 40 cases where jaundice developed while using the oral contraceptives and 13 of their women (32.5%) also had jaundice while pregnant (11). It is, therefore, important that physicians again recognize the fact that women with liver disease, or women who have jaundice or itching while they are pregnant, are also very prone to develop jaundice if they are given oral contraceptives, and this then represents a clear contraindication to their usage. Fortunately, dicontinuing the drug usually rapidly "cures" the patient (12). Finally, it should be pointed out that no deaths have been reported from liver disease in women using oral contraceptives.

It is concluded that several of the metabolic functions of the liver are altered by the steroids of the oral contraceptives, particularly the estrogen portion. The sequaleae of these alterations over long term usage is unknown. The immediate effects include the alteration of several of the laboratory tests used in medical diagnoses. Aggravation of existing liver disease, if present, to the point where jaundice may be seen has also been shown. There is no answer to the query of will permanent liver damage result from the use of the oral contraceptives.

B. Lipids

The lipids or fat in the blood are divided into four major groups: (1) free fatty acids; (2) phospholipids; (3) cholesterol; and (4) triglycerides. These individual lipids are bound to plasma proteins (termed lipo-proteins) and carried in the blood. That way they are transported from the site of formation to the site of use. The blood levels of each lipid depends upon a variety of factors including age, diet, weight, sex, and heredity background. In order to meaningfully study any one of these broad groups, each of the variables must be carefully controlled. The importance of the lipids in disease is principally related to the vascular system.

It has been found that there is an elevation of total blood cholesterol and the low density (light) lipo-protein levels in many individuals who demonstrate clinically symptomatic coronary heart disease (13). A major component of this light lino-protein group is the triglyceride fraction. Thus, cholesterol and triglycerides are suspect to causing vascular disease. It is also known that there is a markedly lower incidence of coronary artery disease in premenopausal women as compared to men of the same age group or postmenopausal women (14). These premenopausal women have ovaries that are producing sex hormones. It has been postulated that (1) the blood lipid levels were altered by ovarian hormones and (2) the lipid levels may be causally related to vascular disease and (3) by altering the ovarian hormone levels in the blood one could prevent or cause serious vascular disease. Accordingly, many investigators

have been conducting experiments on the effects of ovarian hormones in men and postmenopausal women, since they represent the vascular-problem prone groups. Although the results of these studies are not necessarily applicable to the young girl taking oral contraceptives, they do show generally that progesterone has little effect on lipids and that the estrogens lower blood total cholesterol and the "light" (Beta) lipo-protein levels (15).

Less information is available for the premenopausal female using the oral contraceptives. A review of these studies can be divided into the four lipid groupings. Again it should be noted that these published reports involve different drugs, different dosages, and different durations of treatment in varying types of women and accordingly cannot always be compared or the results combined. In 1966 Wynn and Door reported an elevation of free fatty acids in the blood of women taking oral contraceptives (16). More recently (1969) they have been unable to confirm this finding (17). Three other investigators have found normal free fatty acid levels in women using the oral contraceptives (18–20).

The second lipid group is the phospholipids. All of the reports demonstrate an elevation of this group (21–23). This is a heterogenous group of many subtypes of phospholipids. The medical meaning of these reported elevations is only open to speculation. Bolton and co-workers have studied patients with arterial occlusive disease and they have found abnormal blood platelet function (important in blood clotting) which is presumably due to an elevation of the blood phospholipid lecithin (24). Whether the elevation of this lipid in the users of the oral contraceptive is related to their proneness to blood clotting diseases is not known at this time.

The third lipid fraction to be considered is cholesterol. Pincus in his original observations on the oral contraceptive could not demonstrate any change in blood cholesterol (25). Several earlier investigators confirmed this report (18, 19, 23, 26, 27). More recently, four research teams have found elevated cholesterol levels in their subjects using oral contraceptives (25, 28–30). This discrepancy of results can be partially explained on the basis of the different drugs that have been used in these investigations.

There is almost unanimity of opinion among the nine investigating groups measuring blood triglyceride levels in women taking a variety of different oral contraceptives. All but one (27) of the reports demonstrate a significant elevation of this lipid (19, 21–23, 26, 28–31). Indeed Zorrilla and his co-workers have produced similar elevations by giving women only the estrogen component of the oral contraceptive (32). Since these lipids are carried on blood proteins, and since we have already described the ability of estrogens to alter the liver's production of blood proteins, these lipid alterations may be a result of disturbed liver function.

Hazzard and associates have also been concerned with the mechanism by which the oral contraceptive alters blood lipids. The level of blood triglycerides are dependent upon two processes: (1) production in the liver which is medicated by insulin, and (2) a breakdown or destruction at body fat depots which is under the control of fat enzymes. They have investigated both processes and their results suggest that there is both an increased rate of synthesis or production of triglycerides as well as a decreased rate of enzyme destruction at fat depots in a woman taking an oral contraceptive (31). It is apparent that the three metabolic areas under review today (liver-lipids and carbohydrates), are interrelated, and a primary alteration produced in one may manifest itself in the other two.

The medical importance of these blood lipid changes falls into two areas. First, for the patient with an abnormal blood lipid pattern, the oral contraceptive may make her even more abnormal. Zorrilla and associates have reported two women whose blood lipids were elevated before receiving an oral contraceptive and who then developed extremely high and dangerous levels of blood lipids (33). deGennes and colleagues have also reported a patient who had a congenitally high blood lipid pattern and who then developed a stroke while receiving an oral contraceptive (34). Again, as with liver disease, the woman who has a minor abnormality before using the oral contraceptive may develop a major one when she takes the drug. It is important for the physician to know his drugs and his patients before combining them. An interesting observation has recently been reported by Glueck and associates from the NIH. They treated a group of four women having abnormally high blood lipid levels with an isolated progestin and the blood lipids decreased (35). The different responses between premenopausal and postmenopausal women, between estrogens and progesterones, and between normal and abnormal women must all be considered in any study.

The second concern is for those women who are normal before receiving the oral contraceptive. This area again is only open to spectulation as no definite scientific data are available to draw upon. Theoretically, if coronary artery and vascular disease is found in association with elevated blood cholesterol and triglyceride levels, then the production of higher blood cholesterol and triglyceride levels in normal women by use of the oral contraceptive may produce or predispose to vascular disease. Although several investigating groups have warned of this problem (22, 29, 36), it has not been documented to occur. A note of caution should be raised however, in that a requirement of time may be necessary before any permanent structural alteration is manifest. Should ten to twenty years of "hyperlipidemia" be necessary, then the clinical diseases should not be expected at this date.

C. Carbohydrates

In 1963 Waine, Frieden and Caplan reported in an abstract in an obscure medical journal that several of the women they were treating with oral contraceptives for rheumatoid arthritis demonstrated an abnormal blood glucose tolerance test (37). Since that report there have been more than 33 published articles in the world dealing with carbohydrate metabolism in more than 1,633 women using the oral contraceptive for periods ranging from 19 days to more than 8 years. Although an attempt will be made to summarize these data, the same problems are encountered, that is, the reports include many different drugs, dosages, durations of treatment and types of tests. Neverthless, certain information is available and some generalizations can be made.

In prospective studies where the women are tested before taking the drugs and then serially thereafter, the development of elevated blood glucose levels is frequently seen. The incidence of this occurrence is variously reported between 0–100% of the time (37, 38–42).

This discrepancy in the incidence of altered blood glucose levels seems to be dependent upon several factors, and each should be studied in some detail. First, the type of testing that is done is important and in general the more elaborate and sensitive the test, the higher is the reported incidence of abnormal findings. Accordingly, the cortisone stimulated oral glucose tolerance test gave more abnormal results than did the plain oral glucose tolerance test or the intravenous glucose tolerance test. In general, for the group studies of short duration, the fasting blood glucose values are generally normal whereas the tolerance curve becomes abnormal. Second, the duration of time that the oral contraceptive had been taken seems to be important. In those studies where the duration of treatment with the oral contraceptive was several years, the incidence of abnormal results was the highest. In one cross-sectional study by Spellacy and associates of 31 women who had used the oral contraceptive continuously for more than 100 cycles, the incidence of abnormal oral glucose tolerance tests was more than 75% (37). Thirdly, the types of subjects given the oral contraceptive is important. In a presumably normal group of women there are certain characteristics which predispose them to a statistically greater likelihood of developing an abnormal blood glucose level while using the oral contraceptives. These characteristics included: (1) women of older age, (2) those of high parity, (3) those who gain excessive amounts of weight while taking the drugs or those that are obese prior to beginning the drugs; (4) those with a positive family history of diabetes mellitus; and (5) those women who had delivered excessively large infants, for example greater than nine pounds at birth. Fourth, the type of oral contraceptive used seems to be important. Again, this is difficult to evaluate but several points are worth mentioning.

The sequentially administered drugs have a somewhat lower incidence of abnormalities than do the combination type drugs. Admittedly the sequential preparations have been used for a shorter duration of time and the studies of them are fewer in number. Probably of more importance then the way the drugs are combined is the type and dosage of the steroid hormone contained in the oral contraceptive. Clinch and colleagues have recently reiterated the importance of dosage of steroids used in relation to the incidence of abnormal glucose results developing (43). Generally the lower the dose the fewer the side effects as was seen with the previous discussions on the liver and lipids. Of even greater interest to the future of contraception is the type steroid used. Several investigators have recently studied the estrogens and progestins separately. Although the data is still sparce, the results show that several of the estrogens above can elevate blood glucose levels (37, 44). When the progestins are investigated there

is a mixture of results with some causing elevations of blood glucose and others having little or no effect. Finally of those with an effect, it is again related to the dosage of progestin used. For example, both Geshberg et al. and Spellacy et al. have demonstrated that medoxyprogesterone acetate causes an elevation of the blood glucose levels (45, 46). In contrast to this ethylnodiol diacetate (44), progesterone (44, 47) and chlormadinone acetate (48, 49) have been shown to not significantly alter blood glucose. Thus, the dose of estrogen and the type and dose of progestin used in the oral contraceptive would certainly affect the incidence of abnormal glucose results produced in the users.

In addition to the blood glucose levels, other parameters of carbohydrate metabolism have been studied. Wynn and Doar have noted elevated levels of blood pyruvate in 12 of 55 subjects (22%) studied who were taking the oral contraceptives (16). Spellacy and co-workers first noted elevated blood insulin levels in women taking oral contraceptives and subsequently many others have confirmed this finding (37). Since we previously discussed the fact that insulin can increase the production of the blood lipid triglycarides, and since the levels of insulin are elevated in oral contraceptive users, we again can see how one area of metabolism being altered can several others. Spellacy et al. reported that levels of growth hormone in the blood are also elevated in women taking the oral contraceptive and this, too, has been confirmed (37). Therefore, the fact that carbohydrate metabolism has been altered in women using these drugs is no longer doubted. The important remaining questions are (1) are these changes reversible and (2) are they harmful?

There are no complete studies available as to the reversibility of these changes. In short, term investigations of only one to four months duration of treatment, the changes are usually reversible. For the longer duration studies the data is even more meager. This is because of several factors. The subjects discontinue from the studies for a variety of reasons and they can therefore not be located for followup testing, or they refuse to discontinue the drugs so that the reversibility of the alterations can be tested.

Probably the most significant question concerns itself with the possible medical hazards resulting from these alterations in carbohydrate metabolism. This question should be looked at in two parts. First, the patient who has a slightly abnormal carbohydrate metabolism when not taking oral contraceptives may be converted from a latent disease to overt insulin requiring diabetes mellitus if given these drugs (37, 42, 46). There is little controversy about giving the overt diabetic patient the oral contraceptive. The control of her disease may be slightly more difficult with the oral contraceptive, but it can be handled (37, 39).

The final problem concerns the normal subject who is given the oral contraceptive. One clinical finding which may be encountered is the development of a vaginal yeast infection (candida albicans). This problem is significantly more common in oral contraceptive users and probably results from the alterations in carbohydrate metabolism that are produced (37). This is a medical nuisance but not a serious health hazard. The production of diabetes mellitus would be a health hazard. No reliable information is available on this question at this time. Wynn and Doar noted that 13% of their subjects developed a chemical diabetes while taking the oral contraceptive and have warned of this complication as have others (17, 37). Since again we are discussing a theoretical disease occurrence which probably requires many years to develop, there is no answer at this date. An awareness of the problem, persistence of observation, and close followup of the treated patients is obviously necessary.

In conclusion, the data that I have reviewed for you today lends itself into two general areas. First, the scientific area. There are several important points. It should be immediately striking that the conclusions we are drawing come from very small sample sizes. For example, more than 18 million women are presumably using these drugs whereas the liver biopsy reports and the long term carbohydrate studies are based upon 31 women each. Most of the metabolic processes seem to be interrelated as with the liver-lipids and carbohydrates. A primary alteration in one may lead to significant alterations in the others. These alterations have to be considered for two types of populations. The one group are those with an already latent disease status, such as the women with a history of jaundice of pregnancy, abnormally high blood lipids or high levels of blood glucose. This group, although small in number, is particularly prone to develop serious medical complications from the use of the oral contraceptive. The prescribing physicians must be made aware of these facts and they must recognize

these women so that they can be given some other forms of conception control. The larger population will be presumably normal and for them the potential production of serious complications such as liver disease, vascular disease, or diabetes mellitus are only a theoretical speculation at this time.

For the philosophical area of conclusions there are significant lessons to be learned from the past. As new modalities of conception control are introduced into medicine for normal subjects, it is important that ongoing prospective in-depth studies of their toxicity be carried out. In December, 1969 Dr. E. Tyler et al. of Los Angeles published their long term followup of one of the first groups of women in the United States to be given the oral contraceptives. Now after 12 years of use and with a current population of more than 8 million women taking these drugs in this country, they can report on but 176 women using the same drug, but at varying dosages, for only 4 to 10 years (50). The maintenance of a large core group for followup is not easy nor inexpensive, but it must be done to insure the safety of future generations. The studies must follow a pure research design utilizing selected drugs and isolated component steroids at the minimum dosages needed for effectiveness, then in future reviews we will no longer need to refer to "oral contraceptive studies" but to specifics such as the progestin X study of 17 women taking the drug for 36 months time. Only this kind of information is truly meaningful. Practicing physicians must be kept aware of the recent advance sin our knowledge of fertility control so that their patients receive the most effective and safest form of treatment possible. And finally, newer methods of conception control should be developed. The fact that in these studies just related to you, the estrogen component of the oral contraceptive can be implicated in most of the adverse reactions, suggests that the "mini-pill" era of conception control utilizing progestins alone, may be at least a temporary solution to our problems. Continued scientific investigations and communications are imperative.

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(Whereupon, at 1:20 p.m., the committee was recessed, to reconvene subject to the call of the Chair.)

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