Effects of oral contraceptives on carbohydrate metabolism

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SYNOPSIS Longitudinal studies of plasma glucose, non-esterified fatty acids (Nefa), and insulin and blood pyruvate levels during oral and intravenous glucose tolerance tests are described in three groups of women treated with combined oral contraceptive preparations: (A) 91 women tested before and during therapy; (B) 39 women tested during therapy and again after this had been discontinued; and (C) 22 women tested twice during therapy. The mean fasting plasma glucose level was unchanged during therapy. In terms of the total area between the plasma-glucose curve and the abscissa, oral and intravenous glucose tolerance deteriorated during therapy in 78% and 70% of group A women, respectively. Thirteen per cent of group A women developed chemical diabetes mellitus during therapy. In group B, oral glucose tolerance improved in 90% and intravenous glucose tolerance improved in 85% after therapy was discontinued. Group C, with an initial mean oral glucose tolerance similar to that of group B during therapy, showed no significant mean change of oral glucose tolerance on retesting. Mean plasma Nefa levels, both before and after oral or intravenous glucose, were unchanged during therapy in groups A and B. During therapy the mean fasting blood pyruvate level was raised in group A and mean blood pyruvate levels were also higher in both groups during oral and intravenous glucose tolerance tests. The mean fasting plasma insulin levels were unchanged during therapy in both groups, but plasma insulin levels were significantly raised in group A after oral and intravenous glucose. Mean plasma insulin levels during oral and intravenous glucose tolerance tests in group B, however, were not significantly different on and off therapy. It is suggested that the impaired glucose tolerance is ‘steroid diabetes’ caused by raised plasma cortisol (hydrocortisone) levels secondary to the oestrogen component of the oral contraceptive. The clinical consequences of these abnormalities remain to be determined. Some individual case studies are presented which exemplify the metabolic abnormalities described above.

Despite a number of conflicting reports, the balance of evidence indicates that oestrogen-progestogen contraceptives impair glucose tolerance in many women using these drugs (Gershberg, Javier, and Hulse, 1964; Wynn and Doar, 1966; 1969a; 1969b; Spellacy, 1969a; 1969b; Beck, 1969; Beck and Wells, 1969; Second Report on the Oral Contraceptives by the Advisory Committee on Obstetrics & Gynaecology, Food & Drug Administration, USA, 1969). The fasting plasma glucose is not altered in the majority of the users but both oral and intravenous glucose tolerance is impaired (Wynn and Doar, 1966; 1969a and b). Some investigators have found the oral test more noticeably affected than the intravenous (Spellacy, 1969a). We have drawn attention (Doar and Wynn, 1969) to difficulties in interpreting the results of in-tra-

1Plasma glucose is used throughout synonymously with 'blood glucose' and 'blood sugar'.

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venous glucose tolerance tests. The widely used "K" value (the rate constant for the disappearance of glucose from the blood) may be the same for plasma glucose curves of widely different absolute values. As will be seen later, this problem is encountered in the analysis of intravenous glucose tolerance data in oral contraceptive users. It should be mentioned that oral and intravenous glucose are not equivalent in their physiological effects (McIntyre, Holdsworth, and Turner, 1964) and that oral glucose tolerance has been shown to be more impaired than the intravenous test in pregnancy (Benjamin and Casper, 1966a) and in obesity (Morse, Sidorov, Soeldner, and Dickson, 1960).

Apart from hyperglycaemia, alterations are found in the blood levels of other metabolites and hormones related to glucose metabolism in women taking oral contraceptives. These include raised insulin levels (Wynn and Doar, 1969a and b; Spellacy, 1969a and b; Beck, 1969; Beck and Wells, 1969; Yen and Vela, 1968) or depressed insulin levels (Javier, Gershberg, and Hulse, 1968; Wynn and Doar, 1969a and b), increased growth hormone levels (Yen and Vela, 1968; Frantz and Rabkin, 1965; Spellacy, Carlson, and Birk, 1967a; Maw and Wynn, in preparation), increased free and bound plasma cortisol (Sandberg, Rosenthal, and Slauwwhite, 1969; Seal and Doe, 1969), increased circulating thyroxine levels (Goolden, Gartside, and Sanderson, 1967), increased plasma pyruvate and lactate levels (Wynn and Doar, 1966; 1969a and b; Doar, Wynn, and Cramp, 1969). The significance of these findings will be discussed in a later section.

When a cortisone or prednisone glucose tolerance test is carried out in women taking oral contraceptives, a distinct deterioration in glucose tolerance is observed in as many as 45 to 85% of the tested subjects (Javier et al., 1968; di Paola, Puchulu, Robin, Nicholson, and Marti, 1968). Insulin secretion is impaired in these women (Kalkhoff, Kim, and Stoddard, 1969). Kalkhoff and his colleagues have referred to this abnormality as 'acquired subclinical diabetes mellitus'.

As well as the observations listed above relating oral contraceptive usage to altered carbohydrate metabolism, there are a number of studies expressing contrary views. These are reviewed by Spellacy (1969a). It is worth considering some of the possible causes for these other findings. Three factors may be important. The first is that many investigators have studied only small groups of subjects. In 17 out of 24 studies listed by Spellacy, the test group numbered 35 or less. The duration of therapy has been short in many studies, being three months or less in seven out of 24. Bearing in mind the intra-individual variation in glucose tolerance and the many factors which affect it and also the possibility that the effects of steroids may not become apparent for several months or even years, it is clear that reliable conclusions will depend upon studies of adequate numbers of patients with suitable controls. The duration of therapy in the tested group should bear some reasonable relationship to the intended duration of therapy in the population at large, which in general, can be counted in years rather than months.

A third difficulty is the variety of compounds and doses used in oral contraception and the importance of testing all of these combinations. As well as these factors, it is important to consider the age of the patient, the parity, the degree of obesity, the family history of diabetes, and it may also be important to consider racial origin and economic status.

It is not clearly established whether all the effects of oral contraceptives on carbohydrate metabolism are due entirely to the oestrogen, or whether the progestogen itself, or the combination of drugs, contributes to the changes observed. Oestrogens given alone may impair carbohydrate metabolism (Javier et al., 1968; Buchler and Warren, 1966; Goldman and Ovadia, 1969). Evidence on the effects of the progestogens used in contraceptives is sparse and conflicting. Progesterone itself is not used for contraception and there are no detailed studies of its effects on carbohydrate metabolism in man. The progestogens used as contraceptives are derivatives of 19-nortestosterone or of 17α-hydroxy-progesterone. 17α-Alky substitution renders the 19-norsteroids active by mouth. The first clinical use of such compounds was as anabolic steroids. Clinical experience with these drugs is extensive and their many metabolic side effects have been described, including hepatic toxicity (Wynn, Landon, and Kaweran, 1961), effects on carbohydrate (Landon, Wynn, Cooke, and Kennedy, 1962a; Landon, Wynn, Houghton, and Cooke, 1962b; Landon, Wynn, and Samols, 1963) and lipid metabolism (Wynn, 1967) and effects upon the metabolism of cortisol (James, Landon, and Wynn, 1962; Wynn, Landon, and James, 1962). It is of interest that it is in these same aspects of metabolism that concern is being expressed in relation to the oral contraceptives. The progestogens derived from 19-nortestosterone and used as contraceptives are employed in lower dosage than the anabolic steroids. Nevertheless, it would seem necessary to study their metabolic effects if their present use as contraceptives is to continue. Even less is known of the metabolic effects of the 17α-hydroxy-progesterone derivatives in man. These are a relatively new class of compounds and no formal metabolic studies in any depth have so far been reported with them.

When one turns to animal experimentation to elucidate these problems, many contradictory reports emerge (Beck, 1969; Rodriguez, 1965; Haist, 1965). It seems that laboratory animals are not good models for testing the effects of gonadal steroids on carbohydrate metabolism in so far as these effects may not apply to man. Nevertheless,
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Beck (1969) has tried to harmonize the various conflicting reports on the effects of gonadal and contraceptive steroids on metabolism in man and animals. He has attempted to define the structure-activity relationships between the large number of different steroids and combination of steroids used as contraceptives. His interesting thesis is that the partial positive charge at the C5 atom, which is common to mestranol, progesterone, norethynodrel, norethindrone, and chloromadinone, causes the compound to have insulinogenic as well as insulin resistance activities which generally neutralize each other when measured in terms of the disposal of intravenously administered glucose. Introduction of a double bond at the C6 position in the B ring reduces or abolishes the hyperglycaemic effect while preserving the insulinogenic action. Beck's informative review highlights the complexities of the subject and shows that considerable advances can be made by formal studies such as he has undertaken. Knowledge of the structure-functional relationships of steroids as they affect carbohydrate metabolism offers the prospect of safer contraceptives in the future.

Effects of Oral Contraceptives on Oral and Intravenous Glucose Tolerance, Plasma Nefa, and Insulin and Blood Pyruvate Levels

SUBJECTS

Three groups of women were studied. Ninety-one women in group A were tested before and again while receiving oral contraceptive therapy. Thirty-nine women in group B were initially tested during therapy and again after this had been discontinued. Twenty-two women in group C were tested twice during therapy. No subject was a known diabetic or was taking any drug known to affect carbohydrate or intermediary metabolism (excepting oral contraceptives). Details of groups A, B, and C are shown in Table I. The oral contraceptives used are shown in Table II. No attempt was made to perform tests at the same time of the menstrual cycle. All women were advised to consume at least 200 g carbohydrate for three days before their test. Any subject with a diabetic sibling, parent, grandparent, uncle, or aunt was considered to have a family history of diabetes.

<table>
<thead>
<tr>
<th>Table II Drug therapy of group A, B, and C subjects</th>
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<tr>
<td>Group</td>
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<tr>
<td>Ovulen</td>
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<tr>
<td>'Step-up'&lt;</td>
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<tr>
<td>Orthovan</td>
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<td>Norinyl</td>
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<td>Lyndiol</td>
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<td>Gynovlar/Anovlar</td>
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<td>Zildian</td>
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<td>Sequential preparations</td>
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<td>Enavid/Enavid E</td>
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PROCEDURE AND METHODS

Oral (OGTT) and intravenous glucose tolerance tests (IVGTT) were carried out by methods previously described (Wynn and Doar, 1966) using glucose loads of 1-0 and 0-5 g/kg body weight respectively. The interval between the two tests was one to seven days. Plasma glucose was measured by an automated glucose oxidase method (Cramp, 1967), plasma Nefa by the method of Dole and Meinert (1960), blood pyruvate by an automated enzymatic fluorometric technique (Cramp, 1968), and plasma insulin by a double antibody radioimmunoassay method (Samols and Bilkus, 1964). Plasma samples from paired tests off and on oral contraceptive therapy were assayed for insulin in the same experimental run.

ANALYSIS OF RESULTS

Plasma glucose, Nefa, insulin and blood pyruvate levels following oral/intravenous glucose in groups A and B were assessed as the mean levels at each time interval. Intravenous glucose tolerance test K values were calculated from the logarithms of the 30-, 40-, 50-, and 60-minute plasma glucose levels using the method of least squares. A value of 0-95 is conventionally regarded as the lower limit of normal (Lundbaek, 1962). Individual curves were also assessed as the total area between the curve and the abscissa, and the incremental area between the curve and a line drawn horizontally through the fasting baseline. These areas were calculated arithmetically in arbitrary units, assuming straight lines between successive points. We have previously described the use of the total area under the oral glucose tolerance test plasma glucose curve as a graded criterion of oral glucose tolerance,

<table>
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<th>Table I Details of group A, B, and C subjects</th>
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<td>Group A</td>
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<tr>
<td>No. of women</td>
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<td>Mean age (years)</td>
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<tr>
<td>Mean body weight as percentage 'ideal body weight'</td>
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<tr>
<td>Obese women (%)</td>
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<tr>
<td>Mean parity</td>
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<tr>
<td>Positive family history of diabetes mellitus (%)</td>
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<tr>
<td>Mean time (months) on (group A) and off (group B) oral contraceptive therapy</td>
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<td>Mean duration (months) of oral contraceptive therapy</td>
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and currently regard a value of 800 units as the upper limit of normal in women in the age group 20-40 years (Wynn and Doar, 1966). Group C subjects were selected as having an average pyruvate tolerance test glucose area (> 700 units) when first tested and the mean interval between the two tests in this group was seven months. Each subject's degree of obesity was expressed as a percentage of the ideal body weight (Documenta Geigy, 1962).

Standard statistical methods were used, including Student's 't' test for paired data, the product moment correlation coefficient, and analysis of variance (one-way classification). Calculations were carried out on an Elliott 803 computer.

Results

Mean plasma glucose, Nefa, insulin, and pyruvate levels during oral and intravenous glucose tolerance tests in group A and B subjects on and off contraceptive therapy are shown in Figures 1, 2, 3, and 4.

**ORAL AND INTRAVENOUS GLUCOSE TOLERANCE TEST PLASMA GLUCOSE LEVELS**

The mean fasting plasma glucose level was not significantly changed by oral contraceptive therapy in groups A or B. In both groups a significant impairment of oral glucose tolerance was found during therapy. The changes in the orally tested total glucose area in each subject of groups A and B are shown in Figures 5 and 6.

Oral glucose tolerance was relatively impaired by oral contraceptive therapy in 71 of 91 group A subjects (78%) and improved after oral contraceptive therapy was discontinued in 35 of 39 subjects (90%) in group B. The mean oral glucose tolerance test glucose area during therapy in group A subjects (730 ± 94 units) was significantly greater than their mean control value before therapy (663 ± 90 units, P < 0.001).

The mean orally tested glucose area after stopping

\[ \text{Mean ± SD} \]

**Fig. 1** Oral glucose tolerance tested mean plasma glucose, Nefa, insulin and blood pyruvate levels in group A before and during therapy.

In this and subsequent figures, N refers to the number of subjects studied and V to the significance of the mean differences.
therapy in group B subjects (724 ± 128 units) was significantly less than the mean value during therapy (858 ± 139 units, p < 0.001). The mean orally tested glucose area in group C subjects when first tested (848 ± 114 units) fell slightly, but not significantly when they were retested (816 ± 137 units).

Seven of 91 group A subjects had pretherapy orally tested glucose areas of greater than 800 units, indicating chemical diabetes mellitus. In one of these subjects the orally tested glucose area deteriorated strikingly during therapy. The remaining six cases were little affected (Figure 5). Eleven of the remaining 83 group A subjects (13%) developed chemical diabetes mellitus (orally tested glucose area > 800 units) during therapy (Figure 5). Twenty-five of 39 group B subjects (64%) had orally tested glucose areas above 800 units when tested during therapy. Of these, all but one improved after therapy was discontinued, although only 14 achieved areas of < 800 units (Figure 6).

The mean intravenously tested plasma glucose levels during oral contraceptive therapy were significantly greater than their respective control values during the greater part of the curve in both groups A and B (Figures 2 and 4). Abnormally low (<0.95) K values were found in one of 81 group A subjects before, and five subjects (6%) during therapy. Three of 33 group B subjects (9%) had abnormal K values during therapy and one of these remained abnormal after therapy was discontinued. A small, but not significant, mean increase in K value (0.11 ± 1.01) occurred in group A subjects during therapy. The increase of mean K value in group B subjects after therapy was discontinued (0.68 ± 0.85, p < 0.001), however, was highly significant.

The mean control intravenously tested glucose area in group A subjects (1,425 ± 236 units) was increased during therapy (1,554 ± 276 units, p < 0.001); the mean intravenously tested glucose area in group B subjects (1,809 ± 254 units) decreased after therapy was discontinued (1,592 units).
± 312 units, \( p < 0.001 \)). The intravenously tested glucose area increased in 57 of 81 (70%) group A subjects during and decreased in 27 of 32 (85%) group B subjects after therapy was discontinued. A significant correlation (\( r = 0.35, p < 0.01 \)) was found between the changes in orally and intravenously tested glucose areas during oral contraceptive therapy in 72 group A subjects.

No significant correlation between the change in orally or intravenously tested total glucose areas during therapy and age, degree of obesity, parity, or duration of therapy was found in group A or B subjects. Analysis of variance showed that the mean changes in the orally tested glucose area in subjects receiving various oestrogen-progestogen combinations were not significantly different. The mean change in the orally tested glucose area was similar in group A subjects with (53 ± 94 units) and without (82 ± 118 units, NS) a family history of diabetes mellitus.

**Orally and Intravenously Tested Glucose Tolerance Plasma NEFA Levels**

Neither the mean fasting plasma NEFA levels nor the changes following oral or intravenous glucose differed significantly in groups A and B during oral contraceptive therapy from the mean respective control values (Figures 1, 2, 3, and 4).

**Orally and Intravenously Tested Glucose Tolerance Venous Blood Pyruvate Levels**

The mean fasting blood pyruvate level was significantly raised (\( p < 0.001 \)) during oral contraceptive therapy in group A subjects (Figures 1 and 2). In group B subjects, however, the decrease after stopping therapy was small and not significant. Both the mean orally and intravenously glucose tolerance tested pyruvate incremental areas were in general increased during oral contraceptive therapy in groups.
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Plasma glucose

![Graph showing plasma glucose levels with legends: N = 32](image)

Plasma NEFA

![Graph showing plasma NEFA levels with legends: N = 12](image)

Plasma insulin

![Graph showing plasma insulin levels with legends: N = 26](image)

Blood pyruvate

![Graph showing blood pyruvate levels with legends: N = 31](image)

Fig. 4 Intravenous glucose tolerance tested mean plasma glucose, NEFA, insulin, and blood pyruvate levels in group B subjects during and after therapy.

Fig. 5 Changes in orally tested total glucose area in group A subjects after starting therapy. A 45 degree line is shown.

Fig. 6 Changes in orally tested total glucose area in group B subjects after therapy. A 45 degree line is shown.
and B subjects (Table III). It is of interest that certain subjects in group B were found to have abnormal venous blood pyruvate levels as long as six months after oral contraceptive therapy had been discontinued.

**Table III Mean oral and intravenous glucose tolerance tested pyruvate incremental areas off and on oral contraceptive therapy in groups A and B subjects**

<table>
<thead>
<tr>
<th></th>
<th>Mean OGTT Pyruvate Incremental Area (units)</th>
<th>P</th>
<th>Mean IVGTT Pyruvate Incremental Area (units)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Before therapy 0.98 ± 0.58</td>
<td>NS</td>
<td>0.87 ± 0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>During therapy 1.15 ± 0.69</td>
<td></td>
<td>1.20 ± 0.54</td>
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<tr>
<td>Group B</td>
<td>Off therapy 1.07 ± 0.62</td>
<td>&lt;0.001</td>
<td>1.07 ± 0.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>During therapy 1.82 ± 0.98</td>
<td></td>
<td>1.74 ± 1.09</td>
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</table>

ORALLY AND INTRAVENOUSLY TESTED GLUCOSE TOLERANCE PLASMA INSULIN LEVELS

Mean fasting plasma insulin levels were not significantly different on and off oral contraceptive therapy in either group A or B subjects. During oral contraceptive therapy, however, mean plasma insulin levels after oral or intravenous glucose administration were significantly raised above control levels in group A but not in group B subjects (Figures 1, 2, 3, and 4).

BODY WEIGHT

A small but significant increase in mean body weight (1.45 ± 3.8 kg, p < 0.001) occurred in group A subjects during oral contraceptive therapy. A similar reduction in mean body weight (1.24 ± 3.55 kg, p < 0.05) was noted in group B subjects after stopping oral contraceptive therapy. Sixty-nine of 91 (76%) group A subjects gained weight during therapy and 21 of 39 (54%) group B subjects lost weight after therapy was discontinued.

Discussion

In a previous cross-sectional study of 105 women taking oral contraceptives and a control group of 78 women, we found impaired oral and intravenous glucose tolerance, raised plasma Nefas and raised venous blood pyruvate levels both before and after oral and intravenous glucose administration (Wynn and Doar, 1966). The present longitudinal study confirms these findings, with the exception that mean fasting plasma Nefas levels were not affected by oral contraceptive therapy. In addition, we have found mean plasma insulin levels to be raised during therapy after oral and intravenous glucose administration, though the mean fasting plasma insulin level was unchanged. Most of these metabolic changes were reversed after therapy had been discontinued.

No significant change in the mean fasting plasma glucose level off and on oral contraceptive therapy was found in group A or B subjects, confirming findings of previous investigators (Wynn and Doar, 1966; Posner, Silverstone, Pomerance, and Baumgold, 1967a; Posner, Silverstone, Pomerance, and Singer, 1967b; Spellacy, Carlson, Birk, and Schade, 1968a). In two reports (Gersberg et al, 1964; Besch, Voris, Ullery, Stevens, and Barry, 1965) raised fasting plasma glucose levels were found. In some of our subjects who were normal before starting treatment, the fasting plasma glucose level has become abnormally raised during treatment and has returned to normal levels when treatment was stopped (Wynn and Doar, unpublished findings). The proportion of such women cannot be given yet from our prospective study because of its short duration. In 10 patients with maturity-onset diabetes the raised plasma glucose level rose further and the abnormal glucose tolerance worsened after one month's treatment with Ovulen (Goldman and Ovadia, 1969).

The total area under the oral glucose tolerance test plasma glucose curve increased in 78% of group A subjects during therapy. Thirteen percent of group A subjects developed chemical diabetes (oral glucose tolerance test glucose area > 800 units) during therapy, an incidence similar to that reported in our previous study (Wynn and Doar, 1966).

Mean plasma glucose levels were slightly, but significantly raised in group A subjects for the greater part of the intravenous glucose tolerance test plasma glucose curve. While no significant change in the mean intravenous glucose tolerance test K value was found, five subjects (6%) developed abnormal values (< 0.95) during therapy. The mean total area under the intravenous glucose tolerance test plasma glucose curve was significantly increased (p < 0.001) during therapy. The results of previous longitudinal studies of the effects of oral contraceptive therapy on intravenous glucose tolerance are conflicting. Posner et al (1967a, b) found progressively impaired intravenous glucose tolerance in women receiving Enovid, tested at two and four to six months after starting therapy. Spellacy and Carlson (1966), Spellacy et al (1967a), and Spellacy (1969a), using the same drug, noted relatively impaired intravenous glucose tolerance during the first and twelfth cycles, but not during the sixth cycle of treatment. Starup, Date, and Deckert (1968), using a com

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Combination of mestranol and megestrol acetate, observed intravenous glucose tolerance to be unchanged after treatment for one year. These conflicting findings cannot wholly be explained by the use of various oestrogen-progestogen combinations. Interpretation of intravenous glucose tolerance curves is difficult and we regard the K value as an unsatisfactory criterion (Wynn and Doar, 1969a; Doar and Wynn, 1969). In this respect our findings confirm those of Clinch, Turnbull, and Khosla (1969), who found the mean intravenously tested plasma glucose level to be increased during Norinyl therapy, while the mean K value was actually higher. In the present study there was a significant correlation ($r = 0.35$, $p < 0.01$) between the changes in oral and intravenous glucose tolerance (assessed as the total area under the curve) in 72 group A subjects.

No significant correlation was found between the changes in oral or intravenous glucose tolerance area off and on therapy and the subject's age, degree of obesity, change in body weight during therapy, parity, or duration of therapy. The present study, however, was not entirely suitable for analysis of the effect of duration of therapy, since this was similar in the majority of group A subjects. Analysis of variance revealed that the mean changes in the orally and intravenously tested glucose area did not differ significantly with any of the oestrogen-progestogen combinations used. The mean changes in these indices were similar in subjects with and without a family history of diabetes mellitus.

There have been no previous detailed studies of the reversibility of changes in oral and intravenous glucose tolerance during oral contraceptive therapy, and the findings in group B subjects after therapy was discontinued are therefore important. The orally tested glucose area decreased in 90% and the intravenously tested glucose area decreased in 85% of group B subjects. While the magnitude of the changes in the group B subjects was greater than that found in group A subjects before and during therapy, the two groups are not comparable. In general, group B subjects were older, more parous, more obese, and had received oral contraceptives for a longer period. The selection of group B subjects was not wholly random in that certain women were advised to discontinue oral contraceptive therapy on the basis of an abnormal orally tested glucose area. Some improvement in glucose tolerance on retesting might be expected in such a group because of the intraindividual variation in glucose tolerance (McDonald, Fisher, and Burnham, 1965; O'Sullivan and Hurwitz, 1966). This point was further analysed by retesting 22 subjects (group C) who were selected on the basis of an initial mean orally tested glucose area ($848 \pm 114$ units) similar to that of the group B subjects during therapy ($858 \pm 139$ units). When this group, who continued to take oral contraceptive therapy, were retested some months later, there was no significant change in the mean orally tested glucose area. These results show that the improved oral glucose tolerance in group B subjects was due to stopping therapy.

Neither the mean fasting plasma Nefa level nor the mean levels after oral or intravenous glucose were affected by oral contraceptive therapy in group A or group B subjects. While it has been suggested that raised plasma Nefa levels may contribute to impaired glucose tolerance in diabetes mellitus, thyrotoxicosis, and acromegaly (Randle, 1963), the changes in glucose tolerance observed during oral contraceptive therapy cannot be accounted for by this mechanism.

A striking finding was the abnormally high venous blood pyruvate levels during oral contraceptive therapy. Changes in blood pyruvate levels after glucose administration were also assessed in terms of the pyruvate incremental area between the blood pyruvate curve and a line drawn horizontally between the fasting baseline. In group A subjects, both the mean fasting blood pyruvate level and the mean intravenously tested pyruvate incremental area were increased during therapy. In group B subjects, the mean orally and intravenously tested pyruvate incremental areas decreased after therapy was discontinued. The mean fasting blood pyruvate level also fell, but the change was not statistically significant. These results confirm our original cross-sectional study (Wynn and Doar, 1966).

Some workers (Spellacy and Carlson, 1966; Spellacy et al., 1968a and b; Javier et al., 1968; Wynn and Doar, 1969b) have found the mean fasting plasma insulin level to be unchanged during oral contraceptive therapy, though others have found it to be raised (Spellacy et al., 1967a; Yen and Vela, 1968; Hazzard, Spiger, Bagdade, and Bierman, 1969). Spellacy and Carlson (1966) and Spellacy et al. (1967a and 1968a) observed mean plasma insulin levels to be higher than pretherapy levels during the intravenous glucose tolerance test, but Starup et al. (1968) found no change. Yen and Vela (1968) noted higher plasma insulin levels during therapy after oral glucose tolerance tests. Javier et al. (1968) observed similar changes early in treatment, but with prolonged therapy orally tested plasma insulin levels tended to be low in some subjects as glucose tolerance became further impaired, suggesting exhaustion of pancreatic islet secretion. In the present study oral contraceptive therapy was associated with higher mean plasma insulin levels after oral and intravenous glucose administration in group A subjects, suggesting increased peripheral resistance to the actions of insulin. In group B subjects who had received oral contraceptives for a longer time, orally and intravenously tested plasma insulin levels were similar during and after therapy, in spite of improved glucose tolerance on the second occasion. These findings suggest impaired pancreatic release of insulin during
therapy. Further studies, such as the plasma insulin response to intravenous tolbutamide and the ratio of circulating ‘big insulin’ to ‘little insulin’ (Roth, Gorden, and Pastan, 1968), will be needed to evaluate the effects of oral contraceptive therapy on pancreatic islet secretion.

There have been few investigations of the effects of single gonadal steroids on glucose tolerance in premenopausal women. In a series of elegant studies, Goldman, Oradia, and Eckerling (1968) and Goldman and Oradia (1969) found intravenous glucose tolerance to be relatively impaired during therapy with diethylstilbesterol or premarin, but not during progesterone or medroxy-progesterone acetate administration. Pyörälä, Pyörälä, and Lampinen (1967) noted intravenous glucose tolerance to be impaired after two weeks’ treatment with ethinyl oestriadiol and Javier et al (1968) observed impairment of oral glucose tolerance during mestranol therapy. Oral glucose tolerance, however, was improved in 10 of 18 women with endometrial carcinoma or hyperplasia treated with 17α-hydroxy-progesterone caproate (Benjamin and Casper, 1966b). The balance of evidence suggests that the oestrogen component alone can account for the deterioration of glucose tolerance commonly found during oral contraceptive therapy.

Whether these changes are a primary effect of the oestrogen or secondary to increased levels of other plasma hormones such as cortisol, thyroxine, or growth hormone is not known. There are several metabolic patterns shared by non-obese subjects receiving oral contraceptive therapy, non-obese subjects receiving glucocorticoid therapy, and obese non-diabetic subjects (Doar and Wynn, to be published). The fasting plasma glucose level is normal, but oral glucose tolerance is impaired; the fasting blood pyruvate level and/or the increment above the fasting level after glucose administration may be abnormally raised.

Studies of pyruvate metabolism using a sodium L(+)-lactate infusion technique suggest that the abnormally raised oral glucose tolerance test blood pyruvate levels in obesity and during glucocorticoid and oral contraceptive therapy result from a greater than normal proportion of the glucose load passing down the glycolytic pathway to pyruvate and lactate, rather than an impaired rate of clearance of these metabolites from the circulation (Doar et al, 1969; Doar and Cramp, to be published). It is possible that the changes in all three situations result from glucocorticoid excess. Although the greater part of the plasma cortisol elevation during oestrogen therapy is due to an increase in the protein-bound fraction, which has previously been thought to be biologically inactive (Matsui and Plager, 1966), more recent studies suggest that this fraction may exert biological activity in certain organs with protein-permeable vascular beds, such as the liver (Keller, Richardson, and Yates, 1969). Furthermore, it has also been shown that non-protein-bound plasma cortisol levels are increased during oestrogen therapy (Sandberg, 1969; Burke, 1969). While the plasma cortisol levels are normal in obesity, the cortisol production rate is commonly increased (Schteingart and Conn, 1965). Cortisol catabolism by the liver must be correspondingly increased and this might conceivably produce the abnormalities in oral glucose-tolerance tests proposed as described above.

Raised plasma levels of hormones other than cortisol may play a part in the genesis of the changes during oral contraceptive therapy. Spellacy, Carlson, and Schade (1967b) and Yetter and Vela (1968) consider growth hormone to be important in this respect. The changes in plasma glucose and blood pyruvate levels produced by the administration of thyroid hormone (Stamp, Doar, and Wynn, 1969) or growth hormone (Doar et al, 1969), however, bear no resemblance to those found during oral contraceptive therapy. Furthermore, in several subjects we have observed marked deterioration in oral glucose tolerance during oral contraceptive therapy, in the absence of raised plasma growth hormone levels (Maw and Wynn, to be published).

Prolonged longitudinal studies will be necessary to determine whether the metabolic changes associated with oral contraceptive therapy become more marked with time. It should be noted, however, that Spellacy, Buhl, Spellacy, Moses, and Goldzieher (1966b) carried out oral glucose tolerance tests on 31 subjects who had received combined oral contraceptives for more than eight years. Twelve subjects (39%) had abnormal curves and a further 12 subjects (39%) had borderline abnormal curves. While we have shown a marked improvement in oral glucose tolerance shortly after stopping oral contraceptive therapy, we do not know whether this improvement will continue, or even be maintained. The ability to predict which subjects will develop marked impairment of oral glucose tolerance during therapy would be of great value.

In the present study, however, no one characteristic in patients was found useful in this respect.

Individual Case Studies

CASE 1

A.D. (Fig. 7). A nullipara aged 27 with no family history of diabetes had taken Lyndiol 2-5 (lynstenestrol 2-5 mg, mestranol 0-075 mg) for 11 months. She had no symptoms but had gained 5 kg in weight while taking the pill. Her weight was normal, however, (64-4 kg), her ideal body weight being 63-9 kg.

An oral glucose tolerance test showed chemical diabetes with a glucose tolerance area of 983. Blood pyruvate levels were clearly abnormal after glucose administration, but the fasting level was within the normal range (0-40 to 0-80 mg/100 ml). The plasma insulin levels showed a brisk response and the peak...
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Plasma glucose

Before o.c. 59.5Kg
Lyndiol 2.5 11 months 64.4
off o.c. 6 weeks 63.7
off o.c. 3 months 65.9
Chlormadinone 64.6
4 months

Area
878 983 693 658

Plasma insulin

Blood pyruvate

Fig. 7 Oral glucose tolerance, plasma insulin, and blood pyruvate levels in case 1, A.D., aged 27, IBW = 63.9 kg, FHDM no, parity 0.

level was at 60 minutes, corresponding to the peak of the glucose curve.

Six weeks after stopping the contraceptive pill the oral glucose tolerance had improved but was still abnormal (glucose area 878). The fasting blood pyruvate level was abnormally high, but the subsequent values were at the upper limit of normal. High fasting blood pyruvate levels are found commonly when the oral contraceptive is stopped, and the abnormality may persist for three to four months. The plasma insulin levels were somewhat lower than in the first test, reflecting the lower glucose levels.

Three months after stopping the oral contraceptive oral glucose tolerance was normal (area 693) as were the blood pyruvate levels and the plasma insulin levels. It is of interest that the distinct improvement in glucose tolerance, and lowering of plasma insulin and blood pyruvate levels occurred despite a further slight gain in weight to 65.9 kg.

After the third test the patient took chlormadinone acetate 0.5 mg each day for four months and the glucose tolerance study was repeated. This showed no notable features compared with the preceding test except for a rather high plasma insulin level at 30 minutes (180 µU/ml).

The abnormalities in glucose tolerance observed in this patient while taking the oral contraceptive are indistinguishable from those which may be seen during glucocorticoid administration. Neither obesity, family history of diabetes, multiparity, or age, all factors known to affect glucose tolerance, played any part in
this case. The relatively short exposure (11 months) to oral contraceptives was the probable cause for the abnormalities observed. This case also demonstrates that glucose tolerance abnormalities may not revert to normal until a period longer than six weeks has elapsed after stopping the pill.

**CASE 2**

E.M. (Fig. 8), aged 36, para 2, no family history of diabetes, weighed 56·4 kg. Ideal body weight was 55·3 kg. Oral and intravenous glucose tolerance tests with measurement of plasma insulin levels were normal. Two months after taking Anovlar 21 (norethisterone acetate 4 mg, ethinyl oestradiol 0·05 mg) the test was repeated. Body weight was unchanged. The oral and intravenous tests were now both abnormal. Plasma insulin levels were higher than in the initial tests. Six months after stopping Anovlar 21 the oral and intravenous glucose tolerance had returned to normal, and lower insulin levels were found in the oral test. Insulin levels were not measured in the second control intravenous glucose tolerance test.

This patient exemplifies the development of abnormal oral and intravenous glucose tolerance tests.
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Fig. 9 Oral and intravenous glucose tolerance, plasma insulin, and blood pyruvate levels in case 3.

- - - - - On Ovulen for 10 months
- - - - - - On Ovulen for 31 months
- - - - - - Off Ovulen for 3 months
- - - - - - Off Ovulen for 24 months

within two months of taking an oral contraceptive. Neither weight gain, obesity, multiparity, or family history of diabetes contributed to this patient's carbohydrate abnormality.

CASE 3

N.H. (Fig. 9), aged 26, para 3, had no family history of diabetes or suggestive obstetric history. She commenced oral contraceptive therapy with Ovulen (ethynodiol diacetate 1 mg and mestranol 0.1 mg) in July 1964, when her body weight was 52.7 kg, her ideal body weight being 53.8 kg. She had an oral glucose tolerance test four months later and this was normal, the glucose area being 800. The test was repeated at 10 months. The glucose area was unchanged (750). The test was carried out again at 22 months and the glucose tolerance area was also unchanged (780). Her body weight had now increased to 56.9 kg. At 31 months, the oral glucose tolerance showed a diabetic curve, the area being 1,059. Body weight was now 61 kg. An intravenous glucose tolerance test was carried out for the first time and gave a K value of 1.16. The blood pyruvate curve with the oral test showed pathologically high values. In the intravenous test the pyruvate values were high, but not abnormally so. In the oral glucose tolerance test, the plasma insulin levels showed a delayed and attenuated response reaching its peak at 90 minutes. In the intravenous test, the plasma insulin levels were also rather low and the curve was flat.

The oral contraceptive therapy was discontinued and the patient was tested again at five weeks, three months and two years after stopping treatment. Body weight rose progressively and was 62.5 kg at three months and 67.4 kg two years after stopping the pill. Despite this increase in weight the glucose tolerance curve area at each of the three intervals mentioned was normal and was very similar (745, 736, 782). The blood pyruvate curve was normal, and the plasma
insulin levels showed the peak values to be somewhat higher than those observed when the patient was taking the pill, despite the lower plasma glucose levels, and the peak value occurred earlier, namely at 30 minutes, compared with 90 minutes when the patient was taking the pill. The intravenous glucose tolerance curve carried out after the pill had been stopped for three months showed that the K value had increased to 1·78 and the glucose values were substantially lower compared with the test when the patient was taking the contraceptive pill. The blood pyruvate levels were lower during the intravenous glucose tolerance test and the plasma insulin levels were somewhat higher compared with the corresponding test carried out during pill therapy.

This patient exemplifies the development of chemical diabetes manifest by abnormal oral and intravenous glucose tolerance, which developed after 31 months of oral contraceptive therapy with Ovulen, although no abnormality was found after four months, 10 months, and 22 months of contraceptive therapy. Body weight increased progressively during this period and continued to increase after the oral contraceptive was discontinued. Despite the increasing obesity the biochemical abnormalities observed at 31 months were reversed five weeks after stopping treatment and were not observed again when the patient was tested at three months and at two years. The attenuated insulin response seen at 31 months in both the oral and intravenous test is typical of subclinical diabetes mellitus. The high pyruvate values as seen at this time are indistinguishable from those seen in steroid-treated patients.
of considerable interest that in this patient both the insulin secretion and pyruvate metabolism returned to normal when oral contraceptive therapy was stopped, despite the patient's continued gain in weight and the development of frank obesity.

**Case 4**
P.S. (Figs. 10, 11, 12), aged 30, had no family history of diabetes, parity 4, and no unusual obstetric history. This patient had been taking Ovulen for 31 months. Her body weight was 69 kg, her ideal body weight was 70.2 kg. An oral and intravenous glucose tolerance test was carried out on two occasions with a month's interval (oral test) and three days' interval (intravenous test). The oral glucose tolerance was unremarkable and the two curves were similar, the glucose area being 550 and 587. There was a brisk insulin response on both occasions, the peak being at 30 minutes. The blood pyruvate curve was normal and the plasma Nefa levels showed no abnormality. The intravenous glucose tolerance on both occasions
showed an abnormally slow disappearance of glucose, the K values being 0.74 and 0.91. The plasma insulin levels showed a low and prolonged response. The blood pyruvate levels showed no abnormality.

While still receiving oral contraceptives this patient’s oral glucose tolerance was retested with a prior challenge of hydrocortisone (40 mg was given at midnight and at 6:00 am). The following changes were seen in the oral glucose tolerance test: first, the fasting plasma glucose level was raised and the glucose tolerance considerably impaired (glucose tolerance area 993). The plasma insulin levels showed a delayed, prolonged and attenuated response compared with the levels seen in the preceding two tests. The blood pyruvate levels were abnormally raised during the course of the glucose tolerance curve but the fasting level was not affected. There was a definite elevation in plasma Nefa levels.

The oral contraceptive was omitted for one month and the tests were repeated. Two oral glucose tolerance tests carried out at an interval of four days showed slightly lower values than when the patient was on the pill and the insulin levels were considerably lower. The hydrocortisone glucose tolerance test showed that while glucose tolerance was somewhat impaired, it was only marginally outside normal limits for such a test (the glucose area was 851). Plasma insulin levels showed a brisk normal response, contrasting markedly with the levels observed in the corresponding test when the patient was taking the oral contraceptive.

The blood pyruvate and plasma Nefa levels were normal during the two oral glucose tolerance tests and on this occasion the hydrocortisone glucose tolerance test failed to show any increase in either pyruvate or Nefa levels, in marked contrast to the findings in the same test when the patient was also taking Ovulen.

The intravenous glucose tolerance test carried out one month after stopping Ovulen showed a normal curve, the K value being 1.44. The plasma insulin levels were lower than in the corresponding tests when the patient was taking Ovulen.

This patient exemplifies a number of interesting
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metabolic abnormalities. While taking Ovulen her oral glucose tolerance was normal, and her intravenous test abnormal. This apparent discrepancy is seen not uncommonly in patients with a diabetic response to cortisone (Dyck and Moorhouse, 1966). The cortisone glucose tolerance test revealed a distinct deterioration of glucose tolerance while the patient was taking Ovulen, and an attenuated and prolonged insulin response. Kalkhoff et al (1969) have studied this phenomenon extensively and shown its similarity to subclinical diabetes mellitus. They have suggested the term 'acquired subclinical diabetes', for this condition which has been seen in as many as 45 to 85% of oral contraceptive users.

Conclusion

These four cases exemplify some of the effects of oestrogen-progestogen contraceptives on carbohydrate metabolism in man. It will require a detailed investigation on several hundreds of patients to see whether these changes lead ultimately to a clinically manifest disease such as diabetes mellitus. Another important question is whether impairment of glucose tolerance and increased plasma insulin levels will accelerate the rate of development of atherosclerosis (Keen, Rose, Pyke, Boyns, Chlouverakis, and Mistry, 1965; Epstein, 1967; Stout and Vallance-Owen, 1969). Evidence on this point will be difficult to obtain and the answer may only become apparent in 20 to 30 years' time.

A disturbing feature to which we wish to draw attention is that oral contraceptives, because they have official approval, are widely prescribed without there being any real knowledge about their long-term effects on health. A study of the duration necessary on a large population will require an unusual degree of cooperation between doctors and patients.

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