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Blood Pressure And Body Weight During Pregnancy And Oral Contraceptive Treatment

Beryl Ann Chernick

BLOOD PRESSURE AND BODY WEIGHT DURING PREGNANCY AND ORAL CONTRACEPTIVE TREATMENT

by

Beryl Ann Chernick, M. D.
Department of Pharmacology

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ABSTRACT

Early observation of a toxemia-like syndrome in women using oral contraceptives led to a long-term study of blood pressure and weight changes in a large group of patients using norethindrone-mestranol tablets (combined tablet) as first treatment. These parameters were compared during pregnancy and during contraceptive treatment with the combined tablet (433 white patients, 91 Indian patients) or an intrauterine device -- IUD (115 white patients, 95 Indian patients). The characteristics of all patients who could be followed revealed few important differences between patients assigned to the two treatments but differences between races were found; accordingly, data from Indian and white patients were analyzed separately.

Changes in blood pressure and weight during this first treatment were examined within three cycle groupings: 1-5 cycles, 6-10 cycles, over 10 cycles. No statistically significant differences in blood pressure changes were found except that more white patients using the combined tablet than an IUD met the chosen criteria for elevated blood pressure more than once over their whole course of treatment, ($P<0.05$). Patients using the combined tablet were followed much longer on treatment. When the comparison was standardized so that only the first ten cycles of treatment were considered for those patients who had completed at least ten cycles, there was no statistically significant difference between the proportions of patients in each treatment

group who met the chosen criteria for elevated blood pressure. Although no important elevations of blood pressure were observed during contraceptive treatment with the combined tablet in this study, a more rigidly controlled investigation would be necessary to rule out the possibility of such an effect. Regardless of their initial pressures, the proportion of patients using either the combined tablet or an IUD who had elevated blood pressure readings in all three cycle groups was the same. Similar numbers of patients in each group who had elevated blood pressures initially never had elevated pressures throughout contraceptive treatment. In this study, therefore, there was no consistent pattern of blood pressure change during contraceptive treatment.

Great variability in weight changes occurred during contraceptive treatment but at least 35% of all groups of patients had no significant weight gains. Fewer of the white patients who used an IUD moved into a higher weight percentile category during their whole first treatment than either white patients who used the combined tablet or Indian patients who used either treatment. However, the mean weight gains of both white and Indian patients were higher in those who used the combined tablet than in those who used an IUD.

During the first viable pregnancy, more than half of the patients of each race had met the hypertensive criteria for toxemia of pregnancy. Mean maximum weight gains did not differ significantly from the published average of 24 pounds. In white patients there was some relation between interval weight gain and maximum weight gain. About one-half of the patients of both races gained at least 3 lb. in one week, possibly reflecting water retention. Therefore, at least 50% of patients met the hypertensive criteria for toxemia and exhibited a significantly rapid weight gain during the first viable pregnancy. At the same time, however, the diagnosis

of preeclampsia-eclampsia was only recorded on 17% of the charts of the white patients and on 28% of those of the Indian patients.

Scores assigned to changes in blood pressure and weight were always higher during pregnancy than during contraceptive treatment (either combined tablet or IUD).

Increased vascular reactivity may be genetically determined and stimuli such as fluid retention during pregnancy, oral contraceptive therapy, and the normal menstrual cycle may induce such a response. The present study shows that pregnancy favors the manifestation of this hypertensive tendency much more strongly than either endogenous or exogenous hormones in the nonpregnant state.

INTRODUCTION

Toxemia of pregnancy remains a major cause of maternal and fetal mortality and morbidity. The variations of this syndrome occur during pregnancy or the early puerperium and are characterized by one or more of the following signs: hypertension, edema, proteinuria and, in certain severe cases, convulsions and coma. A syndrome of "prehypertensive toxemia" has recently been recognized: the appearance of sudden weight gain with or without detectable edema long before hypertension or albuminuria occur.

Since the recognition in 1956 of the value of progestational steroids as ovulation inhibitors and their subsequent use in combination with estrogens for contraception, a large population of women of child-bearing age is available for observation of the effects of exogenously administered hormones. These medications are similar to the endogenous steroids essential for the endocrine control of pregnancy and the menstrual cycle. In 1962, Brownrigg published a case report of a patient who developed a toxemia-like syndrome while receiving high doses of norethynodrel in combination with mestranol. Soon after, the author recognized a similar syndrome in a woman using a moderate dose of a norethindrone-mestranol compound. This case stimulated our interest in the incidence of such a syndrome in women using oral contraceptives.

The present study was undertaken to determine the incidence of blood pressure and weight changes in Clinic patients (1) using oral contraceptive treatment (e.g. norethindrone 5 mg. in combination with mestranol 0.075 mg. -- Ortho-Novum 5 mg.); (2) using an intrauterine device (IUD), and (3) during the pregnancies of the same patients. The object was to determine whether any clinically useful prediction could be made on the basis of a correlation between the occurrence of elevation in blood pressure and weight during oral contraceptive therapy and during pregnancy.

HISTORY

With advances in medicine towards the control of disease and infant mortality, a continuing high birth rate threatens to populate this planet with people, the majority of whom will not be able to raise themselves above a subsistence standard of living. Medical progress, responsible for increasing man's life span, should now devote itself to the solution of the urgent social, economic and political problems posed by this population explosion. The development and use of safe and effective contraception is a major contribution to the solution of these problems.

Birth control has been defined as any form of intentional limitation of family size (Guter, 1961). It usually refers to the temporary prevention of conception. In the 1950's, a concentrated study of female reproductive physiology supported by expanding knowledge of steroid chemistry produced a contraceptive which could reduce the chance of unplanned pregnancies virtually to zero. Certain basic discoveries were necessary before this striking advance could occur.

In 1930, Collip extracted an estrogenic ester from placenta. Campbell and Collip (1930) reported on the clinical use of this hormone which Collip named 'Emmenin' (1930). It became the first orally active, water-soluble female sex hormone available for therapy. Butenandt first suggested the steroid structure of

the natural estrogens in 1932 (Spence, 1953). This was later confirmed by Bachmann, Cole and Wilds in 1939 (Spence, 1953). Dodds, Goldberg, Lawson and Robinson (1938) demonstrated that the steroid ring was not essential by synthesizing diethylstilbestrol, a powerful, nonsteroidal oral estrogen from stilbene; this synthetic oral medication was a great advance. Inhoffen and Hohlweg synthesized ethinyl estradiol in 1938 to provide an inexpensive oral steroidal estrogen and Doisy isolated several natural steroidal estrogens from pregnant mare urine in 1942 to add another source of supply (Spence, 1953).

The estrogens found numerous therapeutic applications in gynecology. They have long been used in the palliation of primary dysmenorrhea. Sturgis and Albright (1940) reported that the mechanism of the relief obtained is the suppression of ovulation and the prevention of a progestational endometrium. Other workers confirmed that large amounts of natural estrogens would suppress pituitary gonadotropins although breakthrough ovulation occurs if their use is prolonged (Parkinson, McQuarrie, Ellsworth and Stone, 1966). As early as 1936, Zondek showed that estrogen rapidly suppressed gonadotropic function in rats (Spence, 1953). The ability of the estrogens to inhibit ovulation suggested the possibility of their use as a contraceptive agent. This application was rejected, however, because of the unopposed and excessive stimulation of endometrium and breast that would occur (Hamblen, 1960).

Earlier reference to ovulation-inhibiting activity of the ovary was made by Beard who, in 1897, suggested that the corpus luteum prevented further ovulation during pregnancy. The following year, Zschokke observed that removal of the retained corpus luteum in the cow resulted in the prompt resumption of estrus

(Garcia and Pincus, 1964).

Further experiments in inhibition of ovulation were carried out. In 1914, Pearl and Surface noted a drop in egg production in chickens injected with extracts of mammalian corpus luteum (Garcia and Pincus, 1964). Later, Haberlandt, in 1921, produced temporary sterility in rodents by transplanting ovaries of pregnant animals of the same species (Garcia and Pincus, 1964). In 1929, Parkes could not induce ovulation in animals with active corpora lutea. Smith used corpus luteum extracts to inhibit rabbit ovulation (Garcia and Pincus, 1964).

In the early 1930's Corner and Allen, Wettstein and Hartmann (Spence, 1953) Hisaw and Fevold, and Fels and Slotta (Roland, Applezweig, Clyman, Decker and Ober, 1965) all obtained almost pure crystalline preparations of a substance from swine corpora lutea. Wintersteiner completed the purification and determined the empirical formula (Roland et al., 1965). In 1934, Butenandt, with Slotta and Fernholz, determined that the substance was a steroid and they were able to synthesize it from stigmasterol, derived from the soya bean. (Spence, 1953; Roland et al., 1965). The hormone was named progesterone (L. pro, in favour of + gestatio (gestare) to bear) (Kistner, 1964).

By the early 1940's, the therapeutic use of progesterone in gynecology was well accepted and the demand exceeded the supply. Biological extracts gave very low yields and were very costly. In 1944, Marker synthesized progesterone from a sapogenin, diosgenin (Applezweig, 1962), and this led eventually to a marked reduction in the cost of steroid hormones.

Makepeace, Weinstein and Friedman were the first to follow up the

earlier study of Smith using extracts of corpus luteum. In 1937, they demonstrated that pure progesterone could inhibit ovulation in rabbits (Garcia and Pincus, 1964). Astwood and Fevold showed this effect in rats in 1939 (Garcia and Pincus, 1964). It was not until 1953, however, that Pincus and Chang first published a more intensive study of the nature of the action of progesterone and its derivatives and metabolites. In The Control of Fertility, Pincus (1965) suggested that this time lag was due to the diversion of interest from work on reproduction to a maximum effort for 'war' research. In the hormonal field this activity was focussed mainly on the adrenal steroids. His increased work in reproductive physiology from 1950 on was stimulated by an increasing awareness of the importance of the population explosion and increased popularity of birth control as a social cause.

In 1951, Pincus began research in reproductive physiology as a result of Margaret Sanger's influence. Aided by a grant from the Planned Parenthood Federation of America, he and Chang began their intensive studies of the action of progesterone and its derivatives in rabbits (Maisel, 1965). They soon showed that compounds which effectively inhibited ovulation in the rabbit were also active antifertility agents in the rat. Later, the compounds which were most potent were found to be effective in human subjects as well. The results of the animal studies with progesterone were clinically applied, thus ushering in the era of oral contraception by inhibition of ovulation.

At the same time as Pincus was carrying out these animal studies, Rock and coworkers were using progesterone and diethylstilbestrol to produce prolonged amenorrhea or a pseudopregnancy effect in infertile women (Garcia and Pincus,

1964). In 1954, the cyclic administration of progesterone was applied in women (Garcia and Pincus, 1964). In 1955, the first publication of clinical data was made in the Proceedings of the 5th International Conference on Planned Parenthood in Tokyo. Pincus reported that progesterone in high oral dosage would inhibit ovulation but breakthrough bleeding occurred. Pincus, Rock and Garcia reported (1958) that even with the addition of estrogen to the oral progesterone, bleeding occurred erratically. However, the addition of small amounts of estrogen to the 19-nor steroids produced excellent month-to-month regulation of bleeding.

The first 19-nor steroid, 19-nor progesterone, was synthesized in 1944 by Ehrenstein who observed that it acted like progesterone in rabbits (Maisel, 1965). He was interested, however, in some other aspect and merely noted this effect in passing. His discovery was repeated by Djerassi (1952) who found that the removal of the 19-methyl group from progesterone greatly enhanced its oral activity. Actually, the first synthetic progestagen was intended to be an orally-active androgen because testosterone, like progesterone, is relatively ineffective except by injection. In 1938, Inhoffen had found that 17-ethinyl estradiol was a more potent oral estrogen that estradiol. When 17-ethinyl testosterone or ethisterone was prepared, it was noted to have oral progestational activity rather than the expected androgenic action. Djerassi's preparation of its 19-nor analogue, norethisterone or norethindrone, increased its oral potency by a factor of five (Roland et al., 1965). At the same time, Riegel and Colton developed another 19-nor progestagen, norethynodrel (Maisel, 1965).

Norethindrone and norethynodrel were the progestagens used in the early clinical tests by Pincus and Rock. At first, high doses (10 mg.) were used, and, at

that time, some contamination of these steroids by ethinyl estradiol 3-methyl ether (mestranol) occurred. The irregularity in bleeding control was due to the variation in the quantity of estrogen present. When a specific dose of estrogen was added to the progestagen, bleeding could be controlled and, later, it was found that the dose of progestagen could be reduced.

Norethindrone and mestranol and norethynodrel and mestranol were the first combined oral contraceptive compounds to be tested clinically. The first large clinical trials of the effectiveness, acceptability and side effects of "the pill", as it came to be known, were started in Puerto Rico in 1956 under the supervision of Rice-Wray, then Medical Director of Puerto Rico's Family Planning Clinic. A second field trial in Puerto Rico and one in Haiti were also started. By 1960, these studies along with those in the United States by such men as Tyler and Goldzieher were extensive and convincing enough to gain Food and Drug Administration (FDA) approval for the sale of these medications by prescription to the general public. Thus, a contraceptive became available by which a woman could completely control her own fertility with the minor inconvenience of swallowing one tablet daily for 20 days a month.

Studies soon showed that lower doses of the progestagen in "the pill" could be used while still retaining the certainty of contraception. With these lower doses, the amount of estrogen had to be increased to prevent bleeding irregularities. In August, 1961, the first clinic organized in Canada for the study of the effects of norethindrone 5 mg. in combination with mestranol 0.075 mg. was opened at Victoria Hospital, London, Ontario. This compound was approved by the Food and Drug Directorate for sale in Canada in June, 1962.

Reports of the clinical studies carried out with these medications are very numerous. They have also been extensively reviewed by the lay press. To attract attention rather than to inform its readers, the press unfortunately has too often seized upon the sensational and, therefore, newsworthy aspects of any medical report and thus has evoked undue alarm and psychological distress in the public. Legitimate concern is expressed in medical circles over possible long-term effects of a medication used by large numbers of healthy women of childbearing age to space their offspring. Studies are in progress of all conceptions occurring after the mother has used oral contraception. Concern also centers on the woman whose family is considered complete and who may contemplate the use of this method of contraception for the next 20 years or more.

Alarming publicity first occurred in the summer of 1962 when fatal thromboembolic disease was reported in women using norethynodrel with mestranol. The FDA in the United States set up an Ad Hoc Committee for the Evaluation of a Possible Etiologic Relation with Thromboembolic Conditions. This Committee found no increased incidence of thromboembolic death associated with the use of norethynodrel and mestranol when compared with the incidence in nonpregnant women of childbearing age (FDA Committee, 1963).

By 1965, the FDA estimated that five million American women and two million women in other countries were using this method of contraception (WHO Scientific Group, 1966). Disease, and, in some cases, serious disturbances have been reported in almost every body system of these women. In 1965, a Scientific Group was convened to advise the Director-General of the World Health Organization (WHO) on clinical aspects of the use of these oral hormones. The

chairman of the Group was Sadusk, then the Medical Director of the United States FDA. The report of this committee (1966) pointed out that "in view of this widespread use it is to be expected that many diseases, common as well as rare, to which women in general are subject, will also be encountered among oral contraceptive users. When, in a woman using oral contraceptives, such disease becomes manifest, there is naturally a tendency to assume that this is a consequence of the treatment. Unless the biological mechanism of a side-effect has been established, it is essential in evaluating the possible harmfulness of oral contraceptives to take into account the incidence of the disease in comparable women who do not use these agents. Thus a cause-and-effect relationship should only be accepted when the disease is encountered significantly more frequently among oral contraceptive users than among non-users or when adequate experimental data confirm such a relationship. Failure to do this by either method has been all too conspicuous in many isolated reports of various diseases occurring among women using oral gestogens, although the possible 'early warning' value of such reports is not denied. The importance of individual idiosyncrasies must not be overlooked and deserves further exploration." Furthermore, among its general conclusions, this committee stated: "Laboratory studies of users of oral contraceptives have revealed a number of deviations from established norms, but few, if any, of these appear to have pathological significance. Serious adverse experiences of various kinds, such as thromboembolic phenomena, have been reported in users of oral contraceptives, but no cause-and-effect relationship has been established either by available statistics or by experimental evidence."

Goddard, who succeeded Sadusk in the FDA, felt that the Scientific

Group had "white-washed" the oral contraceptives (Tyler, 1966). Accordingly, he organized the Advisory Committee on Obstetrics and Gynecology to the FDA. Its "Report on Oral Contraceptives", released in August, 1966, which also considered "the pill" in relation to metabolic effects, thromboembolic diseases and cancer agreed in all aspects with the WHO Group. It concluded that there is "no adequate scientific data proving these compounds unsafe for human use." It did say that there are possible theoretical risks and recommended studies to acquire more facts about users of oral contraceptives and to improve surveillance of the drugs. However, it also recommended discontinuance of the time limitations of contraceptive drugs which have already been cleared by the FDA.

Mechanism of Action

Physiological effects other than mechanism of contraceptive action are reviewed in the Discussion particularly as they relate to the results of the present study.

The combined contraceptive tablets are thought to have three main antifertility effects (Tyler, 1966).

1. Inhibition of ovulation is the main and most important action. While there has been some discussion as to how this occurs (Pincus, 1965), it is generally agreed that the interference is at the pituitary-hypothalamic level preventing secretion of luteinizing hormone (Roland et al., 1965). Venning suggested a direct inhibitory action on the ovarian follicles preventing maturation (Pincus, 1965). In 1962, Goldzieher, Moses and Ellis found an elevated luteal phase pregnanediol excretion in 6.8 percent of women using norethindrone 10 mg. with mestranol suggesting the possibility of ovulation and corpus luteum formation. Occasionally it is possible,

however, to have an increased pregnanediol output following adrenocortical stress or from elevated theca cell secretion in the absence of ovulation (Pincus, 1965).

2. Cervical hostility to sperm penetration is produced by alteration of the chemical and physical properties of the cervical mucus (Pincus, 1965; Roland et al., 1965; Tyler, 1966).

3. Distortion of the endometrium would inhibit nidation of any fertilized ovum present (Roland et al., 1965; Tyler, 1966). Serial endometrial biopsies have shown the production of a rapid secretory phase early in the cycle, followed by involution accompanied by stromal stimulation to edema with predecidual formation (Pincus, 1965; Roland et al., 1965).

SEQUENTIAL CONTRACEPTION

The ability of exogenous estrogen alone to prevent ovulation by pituitary gonadotropin inhibition has been applied in therapeutics for at least 25 years. Cyclic sequential use of estrogen in the first two weeks after menstruation followed by one week in combination with oral progesterone was used in the treatment of dysmenorrhea and other gynecological problems. The use of estrogen as a possible contraceptive was overlooked because of fears of the effects of endometrial hyperplasia from unopposed estrogen stimulation. The late addition of progesterone was too expensive to be practical because oral administration is relatively ineffective. Once combined estrogen-progestagen medication was accepted, further ways of reducing side effects and cost were sought.

Cyclic sequential use of estrogen and progestagen was considered to be a more physiologic means of conception control (Parkinson et al., 1966). By 1964, cyclic doses of mestranol as low as 0.08 mg. for 20 days were shown to inhibit

ovulation for up to 12 cycles (Board, 1966). Irregular withdrawal bleeding occurred. The addition of 2 mg. of norethindrone to the last six tablets opposed the hyperplastic action of estrogen on the endometrium and induced regular withdrawal bleeding. These tablets were approved for sale in Canada in 1965. The WHO Scientific Group report on "Clinical Aspects of Oral Gestagens" (1966) concluded that on the basis of data then available, the sequential medication was less effective as a contraceptive than the combined type.

INTRAUTERINE DEVICES

In the last quarter of the 19th century, intracervical and intrauterine devices of a variety of shapes and materials were employed but there was a high incidence of infection, perforation and pregnancy. These contraceptives have been described and illustrated by Kisch (1908), Cooper (1928), Robinson (1929) and Stopes (1929).

In 1928, Grafenberg devised a wholly intrauterine modification of an earlier method (Southam, 1964; Consumers Union Report on Family Planning, 1966). More recently synthetic materials like polyethylene have been used in fashioning inexpensive devices in a variety of shapes which could remain in situ indefinitely. The initial insertion is accomplished through a narrow plastic tube instead of by the earlier method of cervical dilatation (Southam, 1964; Tyler, 1966). Barium is impregnated in the polyethylene devices so that they can be visualized radiographically.

Although a variety of mechanisms of contraceptive action of the modern intrauterine device can be demonstrated in animals, the mechanism in humans is still uncertain. Endometrial changes appear to be limited to increased edema and

vascularity (Southam, 1964). Increased tubal and uterine motility speeding ovum transport and expulsion is the basis of the most popular current theory (Southam, 1964; Consumers Union Report on Family Planning, 1966).

Pelvic cramps and bleeding, as well as more serious complications may occur. Expulsion, which may be unnoticed, and pregnancy with the device in situ occur at varying rates depending on the type of device used.

TOXEMIA OF PREGNANCY

This history will be limited to literature dealing with the recognition of the syndrome. Contemporary observations of blood pressure and weight changes occurring during pregnancy are included in the Discussion along with the results of the present study.

Until the last quarter century, the "toxemias of pregnancy" included a wide variety of disorders such as hyperemesis gravidarum and pica as well as eclampsia and its prodromata. Better understanding of the miscellaneous conditions has left eclampsia and preeclampsia as a possible homogeneous syndrome. In 1895, Zweifel called eclampsia the "disease of theories" and it remains so today. The numerous theories of etiology have recently been reviewed and brought up to date in Williams Obstetrics, (Eastman and Hellman, 1965) and will not be considered here.

The name, eclampsia, was derived from the Greek "to flash or shine out" because of its apparently sudden onset (Kosmak, 1922; DeLee, 1924). In 1763, Boisier de Sauvage differentiated the condition from epileptic seizures by the term 'eclampsia parturientium' (Dexter and Weiss, 1941). François Mauriceau, a French accoucheur of the late 17th century, recognized that the convulsions occurred more

frequently in a first pregnancy (Cianfrani, 1960). In the late 18th century, Alexander Hamilton of Edinburgh described convulsions as well as their immediate prodromata. He was the first to blame the practitioner if convulsions occurred (Kerr, Johnstone and Phillips, 1954). In 1811, John Burns of Glasgow described the syndrome known a century later as preeclampsia, including headache, edema, giddiness, and visual disturbances. He prescribed treatment for this stage as prophylaxis against the convulsions which followed (Kosmak, 1922).

Rayer of Paris noted the frequent appearance of albumen in the urine of apparently healthy pregnant women in 1840 (Dexter and Weiss, 1941; Kerr et al., 1954). The important observation associating albuminuria with puerperal convulsions was made almost simultaneously by Simpson in Edinburgh (Kerr et al., 1954) and Lever in London (1843). From his clinical research, Lever suggested testing the urine at intervals in pregnancy to predict those patients who might later convulse. Although Lever's interest in the problem was first aroused by the resemblance of edema in pregnancy to Bright's disease (Kerr et al., 1954), his discovery that the albuminuria associated with puerperal convulsions always disappears became a major point for differentiating the two conditions (Thoms, 1935). Despite Lever's separation of puerperal convulsions and Bright's disease, eclampsia was later considered a form of this disease, thus classifying with the toxemias all forms of renal disease occurring in pregnancy (Page, 1953).

In 1896, Riva-Rocci and Hill and Barnard, independently, developed a practical method of measuring blood pressure clinically (Page, 1953). This discovery led to a concept of 'preeclampsia', i.e., hypertension, proteinuria and subjective symptoms preceding the eclamptic attack. This concept, presaged by

Lever half a century earlier, led to an interest in prenatal care.

In Edinburgh, the United States and Australia in the early years of the 20th century, outdoor clinics for pregnant women were opened and hospital beds were designated for "prematernity" patients (Kerr et al., 1954). Women were then seen earlier in pregnancy and before the advent of the severe signs of late preeclampsia and eclampsia. These observations led to the discovery that pre-eclampsia was very much commoner than eclampsia (Page, 1953). Some women were found to have an elevated blood pressure before and throughout their pregnancy and, thus, "essential hypertension" was added to the list of toxemias.

Although Lever had described the importance of edema of the face, eyelids and hands occurring in pregnancy and associated with albuminuria, little emphasis was placed on this early sign of preeclampsia until the 1920's. De Lee (1924) recognized that some edema of the feet, hands, or face occurred in more than 50 percent of pregnancies. Edema present in the morning or real anasarca was always pathological and usually preeclamptic.

Since then, it has been recognized that the edema of preeclampsia is a late manifestation of extravascular, extracellular sodium and fluid retention, the earliest sign of which is a rapid weight gain (Chesley, 1944). (Other references are included in the Discussion). This recognition of the early signs of toxemia of pregnancy has been the result of increased prenatal observation. In the first forty years of the 20th century regular prenatal care contributed the most to the improvement in maternal and perinatal morbidity and mortality (Dexter and Weiss, 1941).

Further improvement in this mortality rate was achieved only by turning to prophylaxis and the prevention of eclampsia. In 1947, an experiment was started

in Australia to try to prevent eclampsia (Kerr et al., (1954). All pregnant patients were given meticulous prenatal care with careful control of blood pressure and weight gain. In 1951, Hughes, Dawson and Hamlin reported a marked decline in the incidence of eclampsia in patients treated in this way. Dawson pointed out that as eclampsia is the terminal catastrophe of toxemia, physicians should always heed this clear warning. With adequate prenatal supervision the incidence of eclampsia can be reduced to zero. The incidence of eclampsia in women delivering at the Rotunda in 1836 was one in 600 cases (Kerr et al., 1954). In Australia between 1936 and 1948, the incidence was one in 400 but by 1953, with the new approach to this condition, the incidence was reduced to one in 15,000.

A further 15 years' experience with intensified prenatal care has led to the recognition of very early signs, such as excessive weight gain, which might lead to preeclampsia. Where attention is directed to the prehypertensive phase of the syndrome, its incidence is also falling, resulting in a reduction in maternal and fetal morbidity and perinatal mortality.

METHOD

In August, 1961, a clinic was opened at Victoria Hospital, London, Ontario for the investigation of the effects of a new oral contraceptive. All patients who received contraceptive advice at this clinic until June 1966 were included in at least one part of the present study.

Cyclic use of norethindrone, 5 mg., in combination with mestranol, 0.075 mg., tablets (Ortho-Novum 5 mg. - Ortho Pharmaceutical Co. of Canada Ltd.) was the exclusive method (Appendix A) prescribed until August, 1964, when an intrauterine device (IUD) became available for testing. From March to August, 1965, all new patients requiring or preferring an oral contraceptive were started on the cyclic use of mestranol 0.08 mg. in sequence with norethindrone 2 mg. (Ortho-Novum SQ) instead of the 5 mg. combined tablet (Appendix A). In November, 1965, all patients using this sequential routine were changed over to the combined form because the latter provided greater contraceptive safety.

Patients treated in the Outpatient Department of Victoria Hospital are, in general, from low-income, poorly educated families. Many are supported by welfare funds and raise their children in a variety of conjugal situations. Data obtained from North American Indian women from the Muncey and Southwold Reserves as well as from those living in the city were considered separately from

the data from the white patients. The term, "white patients" will be used throughout the thesis to designate all those who were neither Negro, North American Indian, nor Oriental.

Most patients were started on the chosen contraceptive routine about the time of the six-week postpartum examination. All patients received an initial physical and gynecological examination with a Papanicoulaou smear study. Pelvic examination and cytology were repeated every six months, but none of the pathology or cytology studies will be considered here.

For the first year, the Clinic was conducted by Dr. D.P. Swartz who saw a total of 44 patients and was concerned mainly with contraceptive efficacy and menstrual function (Swartz, Walters, Plunkett and Kinch, 1963). Body weight was recorded at each visit and symptoms were noted. In the second year, the Resident in Obstetrics and Gynecology at Victoria Hospital continued these observations but added routine blood pressure recordings at the suggestion of the author. From July, 1963 to June, 1966, the author personally interviewed each patient when physically possible at each visit. Body weight and blood pressure were recorded as described below, along with the cycle of treatment and the cycle day.

An initial obstetrical and gynecological history was taken and the patient's height measured. After a discussion of contraception and the advantages and disadvantages of available methods, a choice was made according to the patient's desires and prejudices and the physician's judgment. Random allocation to an oral or intrauterine method was impossible within the bounds of providing good medical care. Despite this limitation, once they became available, the group of patients

using an IUD was considered as a "nonmedicated control" group drawn from the same population and observed in the same way as the Clinic patients using oral contraception.

Detailed oral and written instructions in the use of the chosen contraceptive were given and careful records of each patient were maintained (Appendix A). All tablets were handed to the patient by the physician. Daily tablets were taken for 21 days beginning on the fifth day of the menstrual cycle until a more convenient 20-tablet package became available. If postpartum amenorrhea persisted, or the cycle day was inappropriate when the patient presented herself for oral contraception, a five-day course of two daily combined tablets was usually given to induce initial withdrawal bleeding. If the patient requiring an IUD were more than six weeks postpartum, the device was inserted only at the time of menstrual flow. Patients using this latter method were advised to expect some menstrual irregularities in the early months of treatment, whereas patients using the combined tablet were advised to expect a decreased but regular flow.

All patients were requested to return at the end of the first full cycle of treatment to ensure proper use of the method. Most patients were interviewed at intervals of three months thereafter. Monthly or bimonthly observations were made for up to six months on patients using the sequential medication as well as for other special studies.

Blood pressures were determined once during each visit with the patient in sitting position by means of an adult-size sphygmomanometer, the diastolic pressure being read as the point at which the Korotkov sounds became muffled.

It was thought that the initial weight status of the patient might have some effect on later weight changes. According to Pett and Ogilvie (1957), the mean weight at a given height has been considered the desirable weight with a 10 percent adjustment above or below this weight for variations in body types but they pointed out that, "this 10% variation is a concession to the traditional adjustment made with all tables of weights but it has no clear validity, mathematically or physiologically." They considered that a mathematical approach to the variability in body type would be to use the weight percentiles published in their report. From the results of their study, they also considered that skinfold measurement could be a useful adjunct in assessing adiposity. Because skinfold measurements were not generally available in the present study, the tables of Pett and Ogilvie were used to calculate a ratio of weight percentile to height percentile. It must be remembered that these are only related to average figures and the actual weight levels are probably higher than "desirable" for each percentile given. In the above-mentioned report no mention is made of Indians as any special group within the Canadian population.

Weights and heights of both white and Indian patients were measured with the "Physician's Scale" Balance.

The tables of Pett and Ogilvie (1957) were consulted to determine the percentile categories of the patient's weight and height relative to Canadian women of her age. Pett and Ogilvie pointed out a "dissymmetry" in the weight table towards the heavier weights but their tables ended at the 25th and 75th percentiles. Consequently, in this study, the interval between the 25th and 40th percentiles was subtracted from the 25th and, similarly, the interval between the 60th and 75th percentiles was added to the 75th to create two additional categories.

In order to relate the weight and height percentile categories, three ratios were arbitrarily chosen:
a ratio of 1 was assigned if the patient's weight percentile for age was the same as her height percentile for her age; the ratio was less than 1 if the weight percentile was lower than the height percentile; the ratio was greater than 1 if the weight percentile was higher than the height percentile.

A set of mimeographed forms was designed for recording weight and blood pressure changes and other data during pregnancy and at the time of delivery (Appendix B). All outpatient charts and available inpatient charts on patients whose prenatal care and/or delivery records could be located in the clinics and record rooms of Victoria and St. Joseph's Hospitals were reviewed in order to complete these forms for each clinic patient who received contraceptive advice during the period of study.

A code was devised for transferring all the data recorded during the observations throughout contraceptive treatment as well as the information obtained from the charts about pregnancy performance to a set of 12 punched cards for each subject. Computer programs were written for processing those portions of the data

pertinent to the thesis (Appendix C). They were run on the IBM 7040 Computer at the University of Western Ontario.

For analyses, patients were divided into groups on the basis of the first type of contraceptive that they used in the Clinic. The groups were compared with regard to age distribution, past illness, parity, outcome of the most recent pregnancy and time interval since that delivery, blood pressure, and the ratio of weight percentile to height percentile at the first visit to the Clinic. Indian and white patients were considered separately. These parameters were examined to determine whether any unintentional bias existed in assigning the women to oral or intrauterine contraceptive treatments. The "total white patients" and the "total Indian patients" were compared in the same way.

Age distribution, parity, initial blood pressure, and the ratio of weight percentile to height percentile were reconsidered for patients who were followed at the Clinic on either the combined tablet or IUD as the first treatment. In other words, patients with no follow-up and those using the sequential tablet were excluded. Other medications taken during the course of contraception were considered.

In order to determine the effects of norethindrone 5 mg., in combination with mestranol 0.075 mg. (combined tablet), weight and blood pressure changes for patients using this contraceptive relative to the initial weight and blood pressure categories were compared to the same changes in the IUD groups. In all treatments, three time periods were considered: the first five cycles, the second five cycles and all cycles past the tenth.

In considering blood pressure changes, the concern was with elevation

of blood pressure. Criteria established by the American Committee on Maternal Welfare (Eastman and Hellman, 1965) were accepted as the basis for defining an elevated blood pressure. These included one of the following:

> "systolic blood pressure of 140 mm.Hg or more,
> or a rise of 30 mm.Hg or more above the usual level;
> or a diastolic pressure of 90 mm.Hg or more,
> or a rise of 15 mm.Hg or more above the usual level."

Because the Committee considered that a single recording of blood pressure could be misleading, they specified that the abnormal blood pressure must be noted on at least two occasions at least six hours apart. Because multiple readings were not always available for all patients, the fulfilment of one of these criteria on only one occasion was also tabulated. Because the initial blood pressure reading was not always the lowest one recorded, an interval from the lowest to the highest reading of more than 30 mm.Hg systolic pressure or more than 15 mm. diastolic was considered of interest. Combinations of the pairs of systolic and diastolic criteria were also noted.

In order to establish a background of average blood pressure and weight changes during pregnancy for the Clinic population, these parameters were considered relative to initial values for the first viable pregnancy for all patients who came to the Clinic for contraception during the period of this study. The criteria outlined above were used to assess the blood pressure changes during pregnancy.

In order to compare changes in blood pressure and weight occurring during pregnancy and during contraceptive treatment, scores were assigned to these changes. All scores were based on a scale of 0, 1, and 2.

For weight changes during treatment, a score of 1 was given when:

The weight increased sufficiently to move to the next higher percentile category for that age group.

A score of 2 was assigned during treatment if:

The weight increased sufficiently to move to the second or higher percentile category above the initial category for that age group.

A score of 0 was assigned if:

Weight gain was insufficient to move to the next higher percentile category or if a negative weight change occurred.

At the two extremes of the weight range, i.e., much less than the 25th percentile and much greater than the 75th, additional categories were created so that the scores would accurately reflect weight changes. The interval between the 25th and 40th percentiles was subtracted and the interval between the 60th and 75th percentiles was added to the respective levels.

In pregnancy, a score of 1 was assigned for weight if:

the maximum gain was 25 pounds or more

OR

if an interval gain had occurred equal to or greater than 1.5 lb. in any one week

OR

equal to or greater than 3 lb. in any two-week interval

OR

equal to or greater than 5 lb. in any one month.

A score of 2 was assigned if:

the highest gain in any one week was three pounds or higher.

A score of 0 was given if:

none of these criteria was fulfilled.

Blood pressure, both during treatment and in pregnancy was scored in the same manner.

A score of 1 was assigned if:

the systolic blood pressure was equal to or greater than 140 mm.Hg
OR
the diastolic pressure was equal to or greater than 90 mm.Hg
OR
the systolic pressure increased from the initial value by 30 mm. or more
OR
the diastolic pressure increased by 15 mm. or more
OR
the interval from the lowest to the highest reading was greater than 30 mm. systolic
AND/OR
greater than 15 mm. diastolic.

A score of 2 was assigned if:

the systolic blood pressure was equal to or greater than 140 mm.Hg
AND
the diastolic blood pressure was equal to or greater than 90 mm.Hg
OR
the increase from the initial pressure was equal to or greater than 30 mm. systolic
AND
equal to or greater than 15 mm. diastolic.

A score of 0 was assigned when:

none of these criteria was met.

By this means, a score for changes in blood pressure and a score for changes in weight were assigned for each patient both during her contraceptive treatments, according to cycle groups, and during her pregnancies. The pregnancies were divided into four categories: the first viable pregnancy, the most recent pregnancy preceding the first treatment, all the intervening pregnancies,

and any pregnancies occurring after treatment.

Blood pressure and weight scores were compared both during contraceptive treatment and during pregnancy.

In addition, the scores for blood pressure and weight changes during contraceptive treatment were compared to the scores for changes during pregnancy to determine whether any relation existed between the occurrence of these changes during oral contraceptive therapy and during pregnancy. The same comparison was made for patients who were followed on two treatments.

Similar scoring was applied to patients using the sequential tablet as the first contraceptive treatment (see Appendix D).

A score combining the blood pressure and weight scores described above was devised (combined score) so that the combination of these parameters during treatment and during pregnancy could be compared. Each parameter was assigned a score of 1, 2, or 3, the combination giving a range from 1 to 6.

Original Score				Combined Score
For Blood Pressure		For Weight		
0	-	0	=	1
0	-	1	=	2
1	-	0		
0	-	2		
2	-	0	=	3
1	-	1	=	4
1	-	2		
2	-	1	=	5
2	-	2	=	6

In addition to this main study, a number of special studies on various aspects of the problem were carried out (Appendix E). These are omitted from the body of the thesis because they were peripheral.

Statistical Analyses

The distributions of the various population characteristics considered above were compared by means of Chi Square tests. McNemar's modification of the Chi Square test was applied in comparing the distribution of elevated systolic and elevated diastolic blood pressures within each group and in analysis of the results of the scoring of blood pressure and weight changes. Chi Square tests were used to compare the distributions of patients with identical scores.

Student's "t" test was used to assess the significance of mean changes in weight from the initial value during the first treatment and from an average total weight gain during the first viable pregnancy.

For all of these tests, a P value > 0.1 was considered "not significant", $P < 0.1 > 0.05$ "approached significance" and $P < 0.05$ indicated a "significant" difference.

RESULTS

CHAPTER I: GENERAL DESCRIPTION OF POPULATION IN STUDY.

Between August 1961 and June 1966, a total of 715 patients were started on a contraceptive treatment at the Clinic at Victoria Hospital, London, Ontario (Table I). Of these, 592 were white women, 477 of whom began to use an oral contraceptive and 115 of whom had an IUD inserted. Of 118 Indian women, 95 started an oral regime and 23 had an IUD inserted. Five patients were Negro and because there were so few in this group they were excluded from further analysis. Initial data and follow-up were lacking in 95 women and they were also excluded from further analysis.

Table IIa shows the number of women who had only one contraceptive treatment at the Clinic chosen from the combined tablet or the IUD, and the number of cycles they completed on that treatment. In Table IIb, the numbers of patients with two or three consecutive treatments are tabulated in the same manner while the numbers of patients with two or more nonconsecutive treatments are tabulated in Table IIc. Patients who used the sequential tablet as the first treatment are considered in Table IId.

The reasons for discontinuing or changing contraceptive methods or for not returning to the Clinic are listed in Table III. Some patients are repre-

TABLE I

ANALYSIS BY RACE OF TYPE OF INITIAL CONTRACEPTION

	WHITE		INDIAN		NEGRO	
	Pills	IUD	Pills	IUD	Pills	IUD
	477	115	95	23	4	1
Total	592		118		5	
TOTAL			715			

KEY TO TABLES IIa, b, c, d

These Tables describe the length of follow-up of patients in the study according to the status of the patient at the end of the study.

TABLE IIa

NUMBER OF PATIENTS BY RACE WHO HAD ONLY ONE TREATMENT (COMBINED TABLET OR IUD)

	WHITE		INDIAN	
	Combined Tablet	IUD	Combined Tablet	IUD
STATUS				
New * Patients	10	5	0	2
No Return	67	31	8	1
Discontinued	159 (1446 c.)	39 (150 c.)	22 (152 c.)	5 (17 c.)
Active **	126 (2494 c.)	23 (239 c.)	33 (836 c.)	12 (110 c.)

c. - no. of cycles completed

* New - patients who started the treatment near the end of the study and hence there was no opportunity for follow-up.

** Active - patients who were still participating in the study at the time it was terminated.

TABLE IIb

PATIENTS WITH TWO OR THREE CONSECUTIVE TREATMENTS

CHOSEN FROM EITHER THE COMBINED TABLET OR IUD

Treatment:	WHITE First	WHITE Second	WHITE Third	INDIAN First	INDIAN Second	INDIAN Third
COMBINED TABLET TO IUD						
STATUS						
Discontinued	27 (357 c.)*	13 (15 c.)		6 (93 c.)	2 (6 c.)	
New		3			0	
No Return		6			2	
Active		13 (195 c.)			2 (9 c.)	
IUD TO COMBINED TABLET						
Discontinued	6 (15 c.)	3 (8 c.)				
New		0				
No Return		1				
Active		2 (7 c.)				
COMBINED TABLET TO IUD TO COMBINED TABLET						
Discontinued	6 (176 c.)	6 (29 c.)	1 (2 c.)	2 (69 c.)	2 (13 c.)	1 (1 c.)
Active			5 (40 c.)			1 (9 c.)

* c. - no. of cycles completed

TABLE IIc: PATIENTS WITH TWO OR MORE NONCONSECUTIVE* TREATMENTS BY RACE

Treatment: STATUS	WHITE First (Combined tablet)	Second (Combined tablet)	Third (Combined tablet)	Fourth (IUD)	INDIAN First (Combined Tablet)	Second (Combined Tablet)	Third (Combined Tablet)	Fourth (IUD)
Discontinued	38 (332 c.)	11 (64 c.)	2 (6 c.)	1 (1 c.)	16 (211 c.)	5 (21 c.)	1 (1 c.)	1 (10 c.)
Pregnant Already	3	0	0	0	3	0	0	0
NNo Return	3	3	2	0	2	0	0	0
New		1	0	0		2	0	0
Active		8 (67 c.)	1 (9 c.)	0		4 (59 c.)	0	0
			(IUD)				(IUD)	
Discontinued			1 ** (3 c.)				0	
Active			1 (10 c.)				0	

c/ - no. of cycles completed

** For example, this patient, after two nonconsecutive periods of treatment with the combined tablet, was fitted with an IUD, whose use she discontinued after three cycles.

Treatment:	WHITE			INDIAN		
STATUS	First (Combined Tablet)	Second (IUD)	Third (Combined Tablet)	First (Combined Tablet)	Second (IUD)	Third (Combined Tablet)
Discontinued		7 (18 c.)	1 (1 c.)		6 (13 c.)	2 (13 c.)
Expelled		0			1	
No Return		2	1		2	
New		2	0		00	1
Active		7 (66 c.)	1 (16 c.)		1 (8 c.)	1 (3 c.)

	(IUD)	(IUD)	
Discontinued	5 (37 c.)		
Active		1 (6 c.) (Combined tablet)	
Discontinued		1 (4 c.)	1 (4 c.)
New		1	0
Active		1 (2 c.)	

*Nonconsecutive-variable time intervals separated the treatments because of pregnancy, marital separation, etc.
c. - no. of cycles completed

TABLE IId

NUMBER OF PATIENTS WITH SEQUENTIAL TABLETS AS THE FIRST TREATMENT BY RACE

Treatment:	WHITE First	WHITE Second	WHITE Third	INDIAN First	INDIAN Second
SEQUENTIAL CHANGED TO COMBINED BY CLINIC STATUS					
Active on 2nd treatment	22 (155 c.)	(120 c.)		2 (17 c.)	(12 c.)
Discontinued 2nd treatment	2 (12 c.)	(3 c.)		0 0	0
NONCONSECUTIVE TREATMENTS					
	(Seq.Tab.)	(Com.Tab.)	(IUD)	(Seq.Tab.)	
Discontinued	14 (36 c.)	1 (5 c.)	1 (1 c.)	1 (3 c.)	
Pregnant Already	1	0	0	0	
No Return	5	0	0	1	
Active		1 (3 c.) (IUD)			
New		1			
Active		1 (11 c.)			

c. - cycles completed
Seq. Tab. - Sequential Tablet
Com. Tab. - Combined Tablet

TABLE III

NUMBER OF PATIENTS DISCONTINUING OR CHANGING METHOD OR NOT RETURNING TO CLINIC*

	COMBINED TABLET		IUD		SEQ. TAB.***	
REASONS **	White	Indian	White	Indian	White	Indian
1. unknown	148	22	56	8	10	2
2. fatal accident	1					
3. moved	16	1	2		1	
4. separated	13		3			
5. to private physician	7	1	9			
6. to Reserve nurse		6				
7. hysterectomy	19	4	12	4		
8. tubal ligation	5		1			
9. other illness	4	5	1	2		
10. test or treatment only	9	1			1	
11. to conceive	12	7	1	1	1	
12. pregnant already	3	5	1		2	
13. failure			2	1		
14. IUD expelled			4	3		
15. method unacceptable	2	2		2		
16. patient or family disapproves	2	2	1		1	
17. confused re method	24	7			1	
18. nausea or vomiting	3	2				
19. bleeding	2		11			
20. weight gain	6	1				
21. swelling of extremities	1					
22. headache	1	3			1	
23. premenstrual tension or irritability	10	1	1			
24. depression	7		1			
25. (1 phlebitis) legs ache	7			1		
26. misc. symptoms	4		2	1		

* All patients are included regardless of number of treatments patient had (i.e., more listed here than actual number of patients involved)

** Reasons 2-12 - unrelated to method
Reasons 13-17 - failure or unacceptability of method
Reasons 18-26 - subjective complaints, possibly related to method
Reason 266- includes abdominal pain, backache, moniliasis, skin rash, hair loss

*** Patients still using sequential tablets in November, 1965 were changed to the combined tablet by the Clinic and are not included here.

sented more than once. The reasons are divided into four categories. The first is unknown and includes a large number of patients who left the study or did not return for follow-up. Many of these were patients who used the combined tablet and had left the study before the present author began work at the Clinic. The second group of reasons may be considered incidental and unrelated to the method itself. These include such things as moving out of town, separation of the husband and wife, sterilization, etc., as well as the best reason for discontinuing contraception, that is, to conceive. The third group of reasons may be attributed to failure or unacceptability of the method. Three patients became pregnant with the IUD in situ, one of these with a tubal ectopic pregnancy. A further seven patients chose to discontinue this method of contraception after the IUD was expelled. Four women, after considerable time, complained that the routine of cyclic daily pill-taking was becoming tedious. A large group of patients could not cope with the complexity of the cyclic method or could not or did not return to the Clinic when their supply of tablets ran out. A number of these became pregnant after this had occurred. The fourth group of reasons includes certain symptoms which may or may not be directly the result of the method of contraception. These reasons include nausea or vomiting on the combined tablet, bleeding (mainly from the IUD), weight gain, swelling of the extremities, headache, premenstrual tension or irritability, complaints of depression, aching legs, and miscellaneous symptoms such as abdominal pain, backache, vaginal discharge, skin rash and hair loss. It is possible that many of these symptoms were present before the treatment began or occurred coincidentally with the contraceptive treatment.

Table IV shows the incidence of significant conditions in the past medical history of the patients at the beginning of the first treatment. The seven patients with diabetes were omitted from further consideration in the study because of the known predisposition to toxemia of pregnancy. Women with elevated initial blood pressures were grouped separately and their pressure changes were considered separately. Bases for diagnosing chronic urinary tract disease in a restrospective study of this nature were considered inexact and this diagnosis was ignored. The category of endocrinopathy included women with thyroid disease and a rheumatoid arthritic receiving chronic corticosteroid therapy. Patients with rheumatic heart disease were asymptomatic. The category of mental and neurological diseases included five patients with cerebral palsy and epilepsy as well as those who had had a previous psychiatric hospital admission. Between 60 and 80 percent of the patients in all of the groups had none of the above conditions.

TABLE IV

PAST MEDICAL HISTORY AT BEGINNING OF FIRST TREATMENT

BY TYPE OF TREATMENT AND RACE

	WHITE			INDIAN		
TREATMENT:	All Pills	IUD	Total	All Pills	IUD	Total
Condition *						
Diabetes	3	3	6	1	0	1
Hypertension	3	2	5	3	2	5
Chronic Urinary Tract Disease	10	1	11	3	1	4
Rheumatic Heart Disease	3	0	3	1	0	1
Varicose Veins	26	11	37	4	0	4
Thrombophlebitis	17	4	21	0	0	0
Endocrinopathy	6	2	8	0	1	1
Mental or Neurological Disease	50	10	60	5	2	7
None of the Above Conditions	313 73%	53 62%	366 71%	78 82%	17 74%	95 81%
TOTAL	431	86	517	95	23	118

* See text for more complete explanation

CHAPTER II: COMPOSITION OF TREATMENT GROUPS AT THE ONSET OF THE FIRST TREATMENT FOR ALL PATIENTS AND FOR THOSE WHO WERE FOLLOWED.

Tables V to XII summarize the characteristics of all the patients who came to the Clinic at the beginning of the first treatment. From these tables, comparisons of age, parity, outcome of the most recent pregnancy, time interval since that delivery, blood pressure, and ratio of weight percentile to height percentile were made. Analyses revealed only a few statistically significant differences between patients using the oral and intrauterine methods of contraception within each race. There were, however, some important differences between the total white patients and the total Indian patients.

Table XIII shows the percentage distribution of patients who used other medications during the first treatment. The types of medication considered were anorexics, diuretics and sedatives or tranquilizers, and combinations of these three. Close to 70 percent of each group used none of the above medications while on the contraceptive regime.

Tables XIV to XIX summarize the initial characteristics of patients who were followed in the Clinic during their first contraceptive treatment (combined tablet or IUD). From these tables, comparisons of age, parity, blood pressure and ratio of weight percentile to height percentile were made. Analyses revealed very

few differences in these distributions from those observed in the analyses of the characteristics of all patients coming to the Clinic for contraception.

In the white patients, the age distribution of those using oral contraception was significantly different from the age distribution of those using an IUD (Tables V and XIV). The higher proportion of patients using an IUD who were in the 28- to 35-year old age group contributed the most to the Chi Square.

None of the comparisons showed any significant difference in overall distribution of parity (Tables VI and XV). The finding that more of the total Indian patients than white patients had more than four viable pregnancies approached significance (Tables VII and XVI). Age-specific comparisons of parity revealed only one significant difference. For all patients (Table VII), it was found that more Indian patients than white patients in the 28- to 35-year old group had had more than four viable pregnancies ($P < 0.01$).

More than 70 percent of all the groups of patients had a term pregnancy preceding the first treatment (Table VIII). Analyses showed no differences in the outcome of the most recent pregnancy except that when the total white patients were compared with the total Indian patients, a significant difference in outcome was found ($P < 0.01$). A higher proportion of white patients than Indian patients had an abortion as the outcome of the most recent pregnancy before the contraceptive treatment.

Table VIII also indicates that there were significant differences in the time intervals from the most recent delivery to the beginning of these two kinds of contraceptive treatment. A greater proportion of patients started to use an IUD than the combined tablet in the first six weeks postpartum (white patients, $P < 0.01$; Indian

patients, $P < 0.05$). It is generally preferred not to start patients on an oral contraceptive until six weeks postpartum at which time uterine involution has occurred. When the total white and total Indian patients were compared as to time interval from delivery to the onset of treatment, there was a significant difference ($P < 0.05$). The Indian patients who did come to the Clinic for contraception came closer to the time of their last delivery whereas many white patients came to the Clinic a year or more after the last delivery for contraception.

The blood pressure at the beginning of the first treatment was not known in similar proportions of all groups (Tables IX and XVII). No differences in the distribution of systolic pressures were found except when the total white and total Indian patients were compared. The major part of the Chi Square was contributed by the high proportion of Indian patients who had a systolic pressure of 140 mm.Hg and over. No differences whatever were found in the overall distribution of diastolic pressures.

For purposes of statistical comparison, the patients in each treatment group were divided into those with a systolic pressure of less than 140 mm. Hg ("low"), and those of 140 mm. Hg and over ("high") (Tables Xa and XVIIIa). No significant differences between treatment groups were observed in the distribution of these groupings of systolic pressures. When the total white patients were compared with the total Indian patients, however, there was a significant difference in this distribution of systolic pressures ($P < 0.01$). Moreover, the only significant age-specific differences in the distribution of "low" and "high" systolic pressures occurred between the total white and total Indian patients in the 28- to 35-year olds and in the over 35-year olds. In other words, a higher proportion of Indian

than white patients in the upper age groups had "high" systolic pressures at the beginning of the first treatment.

For purposes of statistical consideration, the diastolic blood pressure was also divided into a "low" group and a "high" group, "low"being less than 90 mm. Hg and "high" being 90 mm. or more (Tables Xb and XVIIIb). No significant differences were found in the overall distributions of diastolic pressures according to these divisions. Again, when age-specific comparisons were made between total white and total Indian patients, there was no significant difference in the distribution of "low" and "high" diastolic blood pressures except in the 28- to 35-year olds where the difference approached significance (Table Xb). In this age group, a higher percentage of Indian patients than white tended to have a "high" diastolic blood pressure.

Further analyses revealed that the diastolic pressure was "high" in significantly more white women than was the systolic ($P < 0.01$) but in the Indian patients, there was no significant difference between the incidence of "high" systolic and "high" diastolic pressures.

Tables XIa and b show the distribution of patients according to their weight and height percentiles for age at the beginning of the first treatment. The numbers along the diagonal line indicate the number of patients for whom the weight percentile for age was the same as the height percentile. Patients above and to the right of this diagonal had a lower weight percentile for age than their height percentile, and similarly, patients below and to the left of the diagonal had a weight percentile greater than the height percentile for their age. IUD's were usually inserted during the general gynecology clinic while tablets were started at a Clinic

specifically designated for that purpose. Consequently, in many patients using an IUD, the height was never measured.

From the figures in Tables XIa and b, the patients were divided into three categories based upon the ratio of weight percentile to height percentile at the beginning of the first treatment. (Tables XII and XIX). A highly significant difference in the distribution of these three categories ($P < 0.001$) was found between the total white and total Indian patients. Inspection of these tables reveals a higher proportion of Indian patients with a ratio greater than 1 and a higher proportion of white patients with a ratio less than 1. Age-specific comparisons of the distribution of the three ratios between all of the total white and total Indian patients attending the Clinic (Table XII) revealed a significant difference in the age group 20 to 27 years ($P < 0.001$). The largest parts of this Chi Square were contributed by the Indian patients with a ratio greater than 1 and by the white patients with a ratio equal to 1. In the 16- to 19-year olds and the 28- to 35-year olds, the difference in the distribution of the ratios approached significance. When patients over 28 years of age in the two races were compared, the difference in the ratios again approached significance.

In patients with a follow-up on the first treatment (Table XIX), the only significant difference between the total white and total Indian patients in the age-specific distribution of the three ratios occurred in the 16- to 19-year olds ($P < 0.05$). The major portion of this Chi Square was contributed by the high proportion of Indian patients in this age group with a ratio greater than 1 and the lower proportion of Indian patients with a ratio less than 1.

TABLE V

PERCENTAGE DISTRIBUTION OF AGE AT THE BEGINNING OF THE FIRST TREATMENT BY TYPE OF TREATMENT AND RACE

	WHITE (N=511)			INDIAN (N=117)		
	All Pills	IUD	Total	All Pills	IUD	Total
Age (years)	N=428	N=83		N=94	N=23	
16-19	18%	15%	18%	27%	13%	24%
20-27	50	40	48	49	52	50
28-35	23	37	25	20	22	20
Over 35	9	8	9	4	13	6

N= number in group

TABLE VIa

PERCENTAGE DISTRIBUTION OF PARITY* OF SUBJECTS AT THE BEGINNING OF THE FIRST TREATMENT BY TYPE OF TREATMENT AND RACE

	WHITE (N=511)					INDIAN (N=117)				
	All Pills		IUD		Total	All Pills		IUD		Total
	A	B	A	B		A	B	A	B	
Parity	N=252	N=176	N=53	N=30	N=511	N=76	N=18	N=16	N=7	N=117
0	2	13	0	0	2 3	4	6	0	0	3 4
1	20	7	19	13	19 8	20	0	19	0	19 0
2-4	58	52	53	47	58 51	41	39	62	57	45 44
>4	20	38	28	40	21 38	35	55	19	43	33 52
not known	0	0	0	0	0 0	0	0	0	0	0 0

TABLE VIb

Parity	All Pills N=428	IUD N=83	Total N=511	All Pills N=94	IUD N=23	Total N=117
0	3	0	2	4	0	3
1	14	17	15	16	13	15
2-4	56	51	55	41	61	45
>4	27	32	28	39	26	37
not known	0	0	0	0	0	0

* Parity - number of viable pregnancies
A - no abortions
B - one or more abortions in addition to number of viable pregnancies indicated
N - number in group

TABLE VII

PERCENTAGE DISTRIBUTION OF AGE AND PARITY AT THE BEGINNING OF THE FIRST TREATMENT BY THE TYPE OF TREATMENT AND RACE

Age (years)	Parity	WHITE (N=511) ALL Pills N=428	WHITE (N=511) IUD N=83	WHITE (N=511) Total N=511	INDIAN (N=117) All Pills N=94	INDIAN (N=117) IUD N=23	INDIAN (N=117) Total N=117
16-19		(79)*	(12)	(91)	(25)	(3)	(28)
	0	8	0	7	16	0	14
	1	45	58	47	36	0	32
	2-4	47	42	46	48	100	54
	>4	0	0	0	0	0	0
20-27		(214)	(33)	(247)	(46)	(12)	(58)
	0	1	0	1	0	0	0
	1	11**	15	12	13	25	15
	2-4	70	70	70	54	67	57
	> 4	18	15	17	33	8	28
28-35		(97)	(31)	(128)	(19)	(5)	(24)
	0	1	0	1	0	0	0
	1	2	6	3	0	0	0
	2-4	40	42	40	5	20	8
	> 4	56	52	55	95	80	92
	Not known	1	0	1	0	0	0
Over 35		(38)	(7)	(45)	(4)	(3)	(7)
	0	3	0	2	0	0	0
	1	0	0	0	0	0	0
	2-4	34	14	31	0	67	29
	> 4	63	86	67	100	33	71

N = number in group

* numbers in brackets refer to numbers of patients in subgroups

** e.g., 11% of the 214 white patients using pills who were in the 20-27 year old age group had only one previous viable pregnancy.

TABLE VIII: PERCENTAGE DISTRIBUTION OF THE OUTCOME OF THE MOST RECENT PREGNANCY AND THE TIME INTERVAL FROM DELIVERY TO THE BEGINNING OF THE FIRST TREATMENT BY TYPE OF TREATMENT AND RACE

		WHITE (N=511)			INDIAN (N=117)		
Outcome	Time Interval	All Pills N=428	IUD N=83	Total N=511	All Pills N=94	IUD N=23	Total N=117
No Pregnancies		(6)*	(0)	(6)	(3)	(0)	(3)
Abortion		(68)	(7)	(75)	(5)	(3)	(8)
	<6 wk.	28**	71	32	40	67	50
	6 wk.-3 mo.	35	29	35	60	33	50
	3 mo.-1 yr.	22	0	20	0	0	0
	>1 yr.	15	0	13	0	0	0
Premature		(47)	(8)	(55)	(3)	(2)	(5)
	<6 wk.	6	38	11	0	0	0
	6 wk.-3 mo.	70	62	69	100	50	80
	3 mo.-1 yr.	13	0	11	0	50	20
	>1 yr.	11	0	9	0	0	0

N - number in group

* numbers in brackets refer to numbers of patients in subgroups

** e.g., 28% of 68 white women using pills who aborted their most recent pregnancy started the first treatment before 6 weeks had elapsed since that abortion.

Outcome	Time Interval	WHITE (N=511) All Pills N=428	WHITE (N=511) IUD N=83	WHITE (N=511) Total N=511	INDIAN (N=117) All Pills N=94	INDIAN (N=117) IUD N=23	INDIAN (N=117) Total N=117
Term		(302)	(65)	(367)	(82)	(18)	(100)
	< 6 wk.	6	17	8	7	28	11
	6 wk.- 3 mo.	63	55	62	64	67	64
	3 mo.- 1 yr.	16	12	15	24	0	20
	> 1 yr.	14	14	14	5	5	5
	not known	1	2	1	0	0	0
Not Known		(5)	(3)	(8)	(1)	(0)	(1)
	< 6 wk.	0	0	0	0	0	0
	6 wk.- 3 mo.	0	0	0	100	0	0
	3 mo.- 1 yr.	0	34	12	0	0	0
	> 1 yr.	60	33	50	0	0	0
	not known	40	33	38	0	0	100

N - number in group

TABLE IX: PERCENTAGE DISTRIBUTION OF BLOOD PRESSURES AT THE BEGINNING OF THE FIRST TREATMENT BY TYPE OF TREATMENT AND RACE

Systolic Pressure (mm.Hg)	Diastolic Pressure (mm.Hg)	WHITE (N=511) All Pills N=428	WHITE (N=511) IUD N=83	WHITE (N=511) Total N=511	INDIAN (N=117) All Pills N=94	INDIAN (N=117) IUD N=23	INDIAN (N=117) Total N=117
80-99		(32)*	(8)	(40)	(5)	(0)	(5)
	40-59	16	0	12	20	0	20
	60-79	84	88	85	80	0	80
	80-89	0	12	3	0	0	0
	90-109	0	0	0	0	0	0
	110 and over	0	0	0	0	0	0
110-119		(213)	(36)	(249)	(45)	(11)	(56)
	40-59	4	0	4	7	0	5
	60-79	58**	58	58	64	91	70
	80-89	34	39	34	27	9	23
	90-109	4	3	4	2	0	2
	110 and over	0	0	0	0	0	0
120-139		(119)	(24)	(143)	(23)	(7)	(30)
	40-59	1	4	1	0	0	0
	60-79	30	25	29	17	0	13
	80-89	44	38	43	57	71	60
	90-109	25	33	27	26	29	27
	110 and over	0	0	0	0	0	0
140 and over		(10)	(3)	(13)	(8)	(2)	(10)
	40-59	0	0	0	0	0	0
	60-79	10	0	8	0	0	0
	80-89	30	67	38	25	0	20
	90-109	60	33	54	75	50	70
	110 and over	0	0	0	0	50	10
Not Known	Not known	(54)	(12)	(66)	(13)	(3)	(16)

N- number in group

* Numbers in brackets refer to numbers of patients in subgroups

** e.g., 58% of 213 white women using pills who had a systolic pressure of 100-119 mm.Hg at the beginning of treatment, had a diastolic pressure of 60-79 mm.Hg

TABLE Xa: PERCENTAGE AGE DISTRIBUTION OF SYSTOLIC BLOOD PRESSURE AT THE BEGINNING OF THE FIRST TREATMENT BY THE TYPE OF TREATMENT AND RACE

Age (years)	Systolic Pressure (mm.Hg)	WHITE (N=511) All Pills N=428	WHITE (N=511) IUD N=83	WHITE (N=511) Total N=511	INDIAN (N=117) All Pills N=94	INDIAN (N=117) IUD N=23	INDIAN (N=117) Total N=117
16-19		(79)*	(12)	(91)	(25)	(3)	(28)
	80-99	17	8	15	16	0	14
	100-119	54	42	53	44	67	46
	120-139	24	33	25	24	33	25
	140 and over	0	0	0	4	0	4
	not known	5	17	7	12	0	11
20-27		(214)	(33)	(247)	(46)	(12)	(58)
	80-99	7**	18	8	2	0	2
	100-119	54	49	49	61	58	60
	120-139	23	24	23	22	25	22
	140 and over	2	3	8	2	0	2
	not known	14	6	12	13	17	14
28-35		(97)	(31)	(128)	(19)	(5)	(24)
	80-99	5	3	5	0	0	0
	100-119	39	48	40	32	40	33
	120-139	33	23	30	32	40	33
	140 and over	4	0	3	26	20	25
	not known	19	26	22	10	0	9
Over 35		(38)	(7)	(45)	(4)	(3)	(7)
	80-99	0	0	0	0	0	0
	100-119	42	0	36	0	0	0
	120-139	50	71	53	25	34	28
	140 and over	3	29	7	25	33	29
	not known	5	0	4	50	33	43

N - number in group

* numbers in brackets refer to numbers of patients in subgroups

** e.g., 7% of 214 white women using pills who were 20-27 years of age at the beginning of treatment had a systolic pressure of 80-99 mm.Hg.

TABLE Xb: PERCENTAGE AGE DISTRIBUTION OF DIASTOLIC BLOOD PRESSURE AT THE BEGINNING OF THE FIRST TREATMENT BY THE TYPE OF TREATMENT AND RACE

Age (years)	Diastolic Pressure (mm.Hg)	WHITE (N=511) All Pills N=428	WHITE (N=511) IUD N=83	WHITE (N=511) Total N=511	INDIAN (N=117) All Pills N=94	INDIAN (N=117) IUD N=23	INDIAN (N=117) Total N=117
16-19		(79)*	(12)	(91)	(25)	(3)	(28)
	40-59	6	0	6	8	0	7
	60-79	49	50	50	56	66	57
	80-89	33	17	31	20	34	21
	90-109	6	16	8	4	0	4
	Not known	6	17	5	12	0	11
20-27		(214)	(33)	(247)	(46)	(12)	(58)
	40-59	3**	3	4	4	0	3
	60-79	48	52	48	41	50	43
	80-89	26	33	27	33	25	31
	90-109	9	6	9	9	9	9
	Not known	14	6	12	13	16	14
28-35		(97)	(31)	(128)	(19)	(5)	(24)
	40-59	1	0	1	0	0	0
	60-79	35	26	33	21	40	25
	80-89	29	32	30	31	20	29
	90-109	16	16	16	37	40	38
	Not known	19	26	20	11	0	8
Over 35		(38)	(7)	(45)	(4)	(3)	(7)
	40-59	0	0	0	0	0	0
	60-79	32	43	33	0	0	0
	80-89	47	43	46	25	33	29
	90-109	16	14	16	25	0	14
	110 and over	0	0	0	0	34	14
	Not known	5	0	5	50	33	43

N-number in group

* Numbers in brackets refer to numbers of patients in subgroups

** e.g., 3% of 214 white women using pills who were 20-27 years of age at the beginning of treatment had a diastolic pressure of 40-59 mm.Hg

KEY TO TABLES XIa AND XIb

Numbers lying along the diagonal line represent the number of patients whose weight percentile and height percentile categories for their age were the same, e.g., in Table XIa, of 428 white patients who started to use pills, there were 12 whose weight was between the 25th and 40th percentiles for their age and also their height was between the 25th and 40th percentiles for their age.

TABLE XIa

DISTRIBUTION OF WHITE PATIENTS ACCORDING TO WEIGHT AND HEIGHT PERCENTILES FOR AGE*

AT THE BEGINNING OF THE FIRST TREATMENT BY THE TYPE OF TREATMENT

Treatment	Weight Percentile For Age	Height Percentile for Age									
		<< 25th**	< 25th	25th-40th	40th-50th	50th-60th	60th-75th	> 75th	>> 75th***	Not Known	Total
All Pills	<< 25th**	8	12	9	9	3	5	5	1	5	57
	< 25th	5	6	4	5	5	3	3	3	3	37
	25th-40th	4	2	12	6	3	5	2	4	1	39
	40th-50th	4	5	4	5	5	6	2	6	2	39
	50th-60th	3	6	8	5	7	8	3	2	1	43
	60th-75th	4	4	4	7	6	12	6	12	4	59
	> 75th	3	4	9	4	4	6	2	6	1	39
	>> 75th***	4	7	13	11	15	17	10	23	7	107
	not known	0	2	0	1	0	1	1	1	2	8
Total No.		35	48	63	53	48	63	34	58	26	428
IUD	<< 25th	1	2	1	0	2	1	0	1	3	11
	< 25th	0	0	2	1	0	1	0	1	0	5
	25th-40th	0	0	1	0	1	0	1	1	2	6
	40th-50th	0	0	1	0	0	0	0	0	2	3
	50th-60th	1	0	1	4	1	0	0	2	2	11
	60th-75th	0	1	0	0	0	2	0	1	0	4
	> 75th	0	0	0	0	0	2	1	3	1	7
	>> 75th	1	1	1	1	3	1	3	9	11	31
	not known	0	1	0	0	1	0	1	0	2	5
Total No.		3	5	7	6	8	7	6	18	23	83

TABLE XIa

DISTRIBUTION OF WHITE PATIENTS ACCORDING TO WEIGHT AND HEIGHT PERCENTILES FOR AGE*

AT THE BEGINNING OF THE FIRST TREATMENT BY THE TYPE OF TREATMENT

Treatment	Weight Percentile For Age	Height Percentile for Age									
		<< 25th**	< 25th	25th-40th	40th-50th	50th-60th	60th-75th	> 75th	>> 75th***	Not Known	Total
All Pills	<< 25th**	8	12	9	9	3	5	5	1	5	57
	< 25th	5	6	4	5	5	3	3	3	3	37
	25th-40th	4	2	12	6	3	5	2	4	1	39
	40th-50th	4	5	4	5	5	6	2	6	2	39
	50th-60th	3	6	8	5	7	8	3	2	1	43
	60th-75th	4	4	4	7	6	12	6	12	4	59
	> 75th	3	4	9	4	4	6	2	6	1	39
	>> 75th***	4	7	13	11	15	17	10	23	7	107
	not known	0	2	0	1	0	1	1	1	2	8
Total No.		35	48	63	53	48	63	34	58	26	428
IUD	<< 25th	1	2	1	0	2	1	0	1	3	11
	< 25th	0	0	2	1	0	1	0	1	0	5
	25th-40th	0	0	1	0	1	0	1	1	2	6
	40th-50th	0	0	1	0	0	0	0	0	2	3
	50th-60th	1	0	1	4	1	0	0	2	2	11
	60th-75th	0	1	0	0	0	2	0	1	0	4
	> 75th	0	0	0	0	0	2	1	3	1	7
	>> 75th	1	1	1	1	3	1	3	9	11	31
	not known	0	1	0	0	1	0	1	0	2	5
Total No.		3	5	7	6	8	7	6	18	23	83

Treatment	Weight Percentile For Age	Height Percentile for Age: << 25th**	< 25th	25th-40th	40th-50th	50th-60th	60th-75th	> 75th	>> 75th***	Not Known	Total
Total Whites	<< 25th	9	14	10	9	5	6	5	2	8	68
	< 25th	5	6	6	6	5	4	3	4	3	42
	25th-40th	4	2	13	6	4	5	3	5	3	45
	40th-50th	4	5	5	5	5	6	2	6	4	42
	50th-60th	4	6	9	9	8	8	3	4	3	54
	60th-75th	4	5	4	7	6	14	6	13	4	63
	> 75th	3	4	9	4	4	8	3	9	2	46
	>> 75th	5	8	14	12	18	18	13	32	18	138
	not known	0	3	0	1	1	1	2	1	4	13
Total No.		38	53	70	59	56	70	40	76	49	511

* Pett, L.B. and Ogilvie, G.F. (1957)

** In each age group the interval between the 25th-40th percentiles was subtracted from the 25th percentile to produce this additional category.

*** In each age group the interval between the 60th-75th percentiles was added to the 75th percentile to produce this additional category.

TABLE XIb

DISTRIBUTION OF INDIAN PATIENTS ACCORDING TO WEIGHT AND HEIGHT PERCENTILES* FOR AGE

AT THE BEGINNING OF THE FIRST TREATMENT BY THE TYPE OF TREATMENT

Treatment	Weight Percentile For Age	Height Percentile for Age									
		<< 25th**	< 25th	25th-40th	40th-50th	50th-60th	60th-75th	> 75th	>> 75th***	Not Known	Total
All Pills	<< 25th**	0	0	2	0	0	0	0	0	0	2
	< 25th	0	1	0	1	0	0	0	0	1	3
	25th-40th	3	0	5	0	0	1	0	1	0	10
	40th-50th	1	0	0	0	1	1	0	0	2	5
	50th-60th	1	0	2	2	0	0	1	0	0	6
	60th-75th	1	2	3	1	2	3	1	2	0	15
	> 75th	0	4	2	1	1	2	0	0	1	11
	>> 75th***	4	5	12	3	5	4	2	3	3	41
	not known	0	0	0	0	0	0	0	1	0	1
Total No.		10	12	26	8	9	11	4	7	7	94
IUD	<< 25th	0	0	1	0	0	0	0	0	0	1
	< 25th	0	0	0	1	0	0	0	0	0	1
	25th-40th	0	0	0	0	0	0	0	0	0	0
	40th-50th	0	0	1	1	0	0	0	0	0	2
	50th-60th	0	0	0	0	0	0	1	1	0	2
	60th-75th	0	1	0	0	0	1	0	0	0	2
	> 75th	0	0	0	0	2	0	0	1	0	3
	>> 75th	0	1	5	1	1	0	1	0	2	11
	not known	0	0	0	0	0	1	0	0	0	1
Total No.		0	2	7	3	3	2	2	2	2	23

Treatment	Weight Percentile For Age	Height Percentile for Age									
		<<25th**	<25th	25th-40th	40th-50th	50th-60th	60th-75th	>75th	>>75th***	Not Known	Total
Total Indians	<<25th	0	0	3	0	0	0	0	0	0	3
	<25th	0	1	0	2	0	0	0	0	1	4
	25th-40th	3	0	5	0	0	1	0	1	0	10
	40th-50th	1	0	1	1	1	1	0	0	2	7
	50th-60th	1	0	2	2	0	0	2	1	0	8
	60th-75th	1	3	3	1	2	4	1	2	0	17
	>75th	0	4	2	1	3	2	0	1	1	14
	>>75th	4	6	17	4	6	4	3	3	5	52
	not known	0	0	0	0	0	1	0	1	0	2
Total No.		10	14	33	11	12	13	6	9	9	117

* Pett, L.B. and Ogilvie, G.F. (1957)

** In each age group the interval between the 25th-40th percentiles was subtracted from the 25th percentile to produce this additional category.

*** In each age group the interval between the 60th-75th percentiles was added to the 75th percentile to produce this additional category.

TABLE XII: PERCENTAGE AGE DISTRIBUTION OF THE RATIO OF WEIGHT PERCENTILE TO HEIGHT PERCENTILE* AT THE BEGINNING OF THE FIRST TREATMENT BY THE TYPE OF TREATMENT AND RACE

Age (years)	Ratio**	WHITE (N=511) All Pills N=428	WHITE (N=511) IUD N=83	WHITE (N=511) Total N=511	INDIAN (N=117) All Pills N=94	INDIAN (N=117) IUD N=23	INDIAN (N=117) Total N-117
16-19		(79)***	(12)	(91)	(25)	(3)	(28)
	< 1	37	42	37	16	0	14
	1	18	17	18	8	0	7
	> 1	44	33	43	52	100	57
	not known	1	8	2	24	0	22
20-27		(214)	(33)	(247)	(46)	(12)	(58)
	< 1	31****	24	30	9	25	12
	1	19	24	20	15	8	14
	> 1	41	21	38	76	59	72
	not known	9	31	12	0	8	2
28-35		(97)	(31)	(128)	(19)	(5)	(24)
	< 1	35	23	32	16	20	17
	1	15	13	14	10	20	12
	> 1	44	22	39	74	60	71
	not known	6	42	15	0	0	0
over 35		(38)	(7)	(45)	(4)	(3)	(7)
	< 1	37	14	33	0	33	14
	1	16	14	16	25	0	14
	> 1	31	43	33	25	0	14
	not known	16	29	18	50	67	58
Totals	< 1	(143)33	(21)25	(164)32	(11)12	(5)21	(16)14
	1	(75)18	(15)18	(90)18	(12)13	(2) 9	(14)12
	> 1	(178)42	(21)25	(199)39	(63)67	(13)57	(76)65
	not known	(32)7	(26)32	(58)11	(8) 8	(3)13	(11)9

N - number in group

* Pett, L.B. and Ogilvie, G.F. (1957)

** Weight Percentile: Height Percentile

*** numbers in brackets refer to numbers of patients in subgroups

**** e.g., 31% of the 214 white patients using pills who were 20-27 years of age at the beginning of treatment had a ratio of less than 1.

TABLE XIII

PERCENTAGE DISTRIBUTION OF PATIENTS USING OTHER MEDICATIONS DURING FIRST TREATMENT BY TYPE OF TREATMENT AND RACE *

	Type of Medication	WHITE Combined Tablets N=331	WHITE IUD N=62	INDIAN Combined Tablets N=77	INDIAN IUD N=22
1.	Anorexic	8	10	10	5
2.	Diuretic	3	0	3	0
3.	Sedative or Tranquilizer	14	14	7	18
	Combination				
	1 & 2	3	2	1	0
	2 & 3	1	1	1	0
	1 & 3	2	2	0	0
	1 & 2 & 3	1	0	1	5
	None of the Above	68	71	77	72

N= number in group

* Some patients included in this table did not have their weights or blood pressures recorded subsequently.

TABLE XIV

PERCENTAGE DISTRIBUTION OF AGE AT THE BEGINNING OF THE FIRST TREATMENT BY TYPE OF TREATMENT AND RACE FOR PATIENTS WITH FOLLOW-UP

Age (years)	WHITE (N=346) Combined Tablet N=293	IUD N=53	Total N=346	INDIAN (N=87) Combined Tablet N=69	IUD N=18	Total N=87
16-19	20%	8%	18%	23%	11%	21%
20-27	49	43	48	48	61	51
28-35	22	42	26	25	22	24
over 35	9	7	8	4	6	4

N - number in group

TABLE XV

PERCENTAGE DISTRIBUTION OF THE PARITY OF SUBJECTS AT THE BEGINNING OF THE FIRST TREATMENT BY TYPE OF TREATMENT AND RACE FOR ALL PATIENTS WITH FOLLOW-UP

	WHITE (N=346)			INDIAN (N=87)		
Parity	Combined Tablet N=293	IUD N=53	Total N=346	Combined Tablet N=69	IUD N=18	Total N=87
0	3%	0%	2%	1%	0%	1%
1	12	14	13	16	14	15
2 - 4	54	49	53	39	59	44
> 4	31	37	32	44	27	40
not known	0	0	0	0	0	0

N - number in group

TABLE XVI: PERCENTAGE DISTRIBUTION OF AGE AND PARITY OF SUBJECTS AT THE BEGINNING OF THE FIRST TREATMENT BY TYPE OF TREATMENT AND RACE FOR PATIENTS WITH FOLLOW-UP

		WHITE (N=346)			INDIAN (N=87)		
Age	Parity	Combined Tablet N=293	IUD N=53	Total N=346	Combined Tablet N=69	IUD N=18	Total N=87
16-19		(59)*	(4)	(63)	(16)	(2)	(18)
	0	9	0	8	6	0	6
	1	37	50	38	44	100	50
	2-4	54	50	54	50	0	44
	> 4	0	0	0	0	0	0
20-27		(144)	(23)	(167)	(33)	(11)	(44)
	0	1	0	1	0	0	0
	1	10**	12	10	12	25	17
	2-4	67	68	68	55	67	58
	> 4	22	20	21	33	8	25
28-35		(65)	(22)	(87)	(17)	(5)	(22)
	0	2	0	1	0	0	0
	1	1	10	3	0	0	0
	2-4	34	38	35	6	20	9
	> 4	62	52	60	94	80	91
	not known	1	0	1	0	0	0
Over 35		(25)	(4)	(29)	(3)	(0)	(3)
	0	0	0	0	0	0	0
	1	0	0	0	0	0	0
	2-4	30	0	29	0	0	0
	> 4	70	100	71	100	0	100

N - number in group

* numbers in brackets refer to numbers of patients in subgroups

** e.g., 10% of the 144 white patients followed on the combined tablet who were 20-27 years of age at the beginning of treatment had one previous viable pregnancy.

TABLE XVII: PERCENTAGE DISTRIBUTION OF BLOOD PRESSURES AT THE BEGINNING OF THE FIRST TREATMENT BY TYPE OF TREATMENT AND RACE FOR PATIENTS WITH FOLLOW-UP PRESSURES RECORDED

		WHITE (N=346)			INDIAN (N=87)		
Systolic Pressure (mm.Hg)	Diastolic Pressure (mm.Hg)	Combined Tablet N=293	IUD N=53	Total N=346	Combined Tablet N=69	IUD N=18	Total N=87
80-99		(24)*	(4)	(28)	(5)	(0)	(5)
	40-59	21	0	18	20	0	20
	60-79	75	100	78	80	0	80
	80-89	4	0	4	0	0	0
	90-109	0	0	0	0	0	0
	110 and over	0	0	0	0	0	0
100-119		(142)	(28)	(170)	(32)	(9)	(41)
	40-59	0	0	1	6	0	5
	60-79	61**	50	58	66	89	71
	80-89	35	46	37	25	11	22
	90-109	4	4	4	3	0	2
	110 and over	0	0	0	0	0	0
120-139		(87)	(15)	(102)	(16)	(6)	(22)
	40-59	1	0	1	0	0	0
	60-79	29	27	28	19	0	14
	80-89	49	27	46	62	67	63
	90-109	21	46	25	19	33	23
	110 and over	0	0	0	0	0	0
140 and over		(9)	(2)	(11)	(8)	(1)	(9)
	40-59	0	0	0	0	0	0
	60-79	11	0	9	0	0	0
	80-89	33	50	36	25	0	22
	90-109	56	50	55	75	0	67
	110 and over	0	0	0	0	100	11
not known	not known	(31)	(4)	(35)	(8)	(2)	(10)

N-number in group

* numbers in brackets refer to numbers of patients in subgroups

** e.g., 61% of the 142 white patients followed on the combined tablet who had a systolic pressure of 100-119 mm.Hg at the beginning of treatment had a diastolic pressure of 60-79 mm.Hg

TABLE XVIIIa

PERCENTAGE AGE DISTRIBUTION OF SYSTOLIC BLOOD PRESSURE AT THE BEGINNING OF THE FIRST TREATMENT BY THE TYPE OF TREATMENT AND RACE FOR PATIENTS WITH FOLLOW-UP BLOOD PRESSURE RECORDED

		WHITE (N=346)			INDIAN (N=87)		
Age (years)	Systolic Pressure (mm.Hg)	Combined Tablet N=293	IUD N=53	Total N=346	Combined Tablet N=69	IUD N=18	Total N=87
16-19		(59)*	(4)	(63)	(16)	(2)	(18)
	80-99	19	25	19	25	0	22
	100-119	52	25	51	38	50	39
	120-139	22	50	24	25	50	28
	140 and over	0	0	0	6	0	6
	not known	7	0	6	6	0	5
20-27		(144)	(23)	(167)	(33)	(11)	(44)
	80-99	6	13	7	3	0	2
	100-119	53**	70	55	61	55	59
	120-139	26	17	25	21	27	23
	140 and over	3	0	2	3	0	2
	not known	12	0	11	12	18	14
28-35		(65)	(22)	(87)	(17)	(4)	(21)
	80-99	5	0	3	0	0	0
	100-119	40	50	43	35	50	38
	120-139	35	32	34	24	50	29
	140 and over	6	0	5	29	0	24
	not known	14	18	15	12	0	9
over 35		(25)	(4)	(29)	(3)	(1)	(4)
	80-99	4	0	3	0	0	0
	100-119	36	0	31	0	0	0
	120-139	56	50	55	34	0	25
	140 and over	4	50	11	33	100	50
	not known	0	0	0	33	0	25

N - number in group

* numbers in brackets refer to numbers of patients in subgroups

** e.g., 53% of the 144 white patients followed on the combined tablet who were 20-27 years of age at the beginning of treatment had a systolic pressure of 100-119 mm.Hg

TABLE XVIIIb

PERCENTAGE AGE DISTRIBUTION OF DIASTOLIC BLOOD PRESSURE AT THE BEGINNING OF THE FIRST TREATMENT BY THE TYPE OF TREATMENT AND RACE FOR PATIENTS WITH FOLLOW-UP PRESSURES RECORDED

Age (years)	Diastolic Pressure (mm.Hg)	WHITE (N=346) Combined Tablet N=293	IUD N=53	Total N=346	INDIAN (N=87) Combined Tablet N=69	IUD N=18	Total N=87
16-19		(59)*	(4)	(63)	(16)	(2)	(18)
	40-59	7	0	6	13	0	11
	60-79	54	75	56	56	50	56
	80-89	25	0	24	19	50	21
	90-109	7	25	8	6	0	6
	not known	7	0	6	6	0	6
20-27		(144)	(23)	(167)	(33)	(11)	(44)
	40-59	1	0	1	4	0	2
	60-79	48**	52	49	45	46	45
	80-89	31	44	33	30	27	30
	90-109	7	4	7	9	9	9
	not known	13	0	10	12	18	14
28-35		(65)	(22)	(87)	(17)	(4)	(21)
	40-59	2	0	1	0	0	0
	60-79	34	23	31	24	50	28
	80-89	32	32	32	35	25	33
	90-109	18	27	21	29	25	29
	not known	14	18	15	12	0	10
over 35		(25)	(4)	(29)	(3)	(1)	(4)
	40-59	0	0	0	0	0	0
	60-79	28	50	31	0	0	0
	80-89	64	25	59	34	0	25
	90-109	8	25	10	33	0	25
	110 and over	0	0	0	0	100	25
	not known	0	0	0	33	0	25

N - number in group

* numbers in brackets refer to numbers of patients in subgroups

** e.g., 48% of the 144 white patients followed on the combined tablet who were 20-27 years of age at the beginning of treatment had a diastolic pressure of 60-79 mm.Hg

TABLE XIX

PERCENTAGE AGE DISTRIBUTION OF THE RATIO OF THE WEIGHT PERCENTILE TO HEIGHT PERCENTILE* AT THE BEGINNING OF THE FIRST TREATMENT BY THE TYPE OF TREATMENT AND RACE FOR PATIENTS WITH FOLLOW-UP

Age (years)	Ratio**	WHITE (N=359) Combined Tablet N=303	IUD N=56	Total N=359	INDIAN (N=91) Combined Tablet N=69	IUD N=22	Total N=91
16-19		(53)***	(5)	(58)	(16)	(2)	(18)
	<1	41	40	41	13	0	11
	1	17	20	17	6	0	6
	>1	40	40	40	56	100	61
	not known	2	0	2	25	0	22
20-27		(150)	(25)	(175)	(33)	(12)	(45)
	<1	32****	20	30	3	25	9
	1	20	24	21	12	8	11
	>1	43	32	41	85	59	78
	not known	5	24	8	0	8	2
28-35		(75)	(21)	(96)	(17)	(5)	(22)
	<1	36	29	34	12	20	14
	1	17	9	16	12	20	14
	>1	44	38	43	76	60	72
	not known	3	24	7	0	0	0
over 35		(25)	(5)	(30)	(3)	(3)	(6)
	<1	48	20	43	0	33	17
	1	12	0	10	34	0	17
	>1	24	60	30	33	0	16
	not known	16	20	17	33	67	50
Totals in each Ratio	<1	(109)36	(14)25	(123)34	(5)7	(5)23	(10)11
	1	(55)18	(9)16	(64) 18	(8)12	(2)9	(10)11
	>1	(124)41	(21)38	(145)40	(51)74	(12)54	(63)69
	not known	(15)5	(12)21	(27)8	(5)7	(3)14	(8)9

N-number in group

* Pett, L.B. and Ogilvie G.F. (1957)

** Weight Percentile: Height Percentile

*** numbers in brackets refer to numbers of patients in subgroups

**** e.g., 32% of 150 white women followed on the combined tablet who were 20-27 years of age at the beginning of treatment had a ratio of less than 1.

CHAPTER III: CHANGES IN BLOOD PRESSURE AND WEIGHT DURING THE FIRST TREATMENT.

The percentage distribution of patients according to the number of cycles they completed during their first treatment is shown in App. Table I*. Approximately 50 percent of all patients in whom these parameters were followed completed less than six cycles. Another 25 percent completed from six to ten cycles.

Table XX shows the number of patients according to the number of cycles completed. From this table, it can be seen that a higher proportion of patients using the combined tablet than using the IUD were followed for more than ten cycles. Also, from App. Table I, it is evident that even in those patients using an IUD who completed more than ten cycles on the first treatment, none completed more than 20 cycles whereas up to 61 cycles were completed by those using the combined tablet.

The percentage distribution of blood pressure elevations (fulfilment of the criteria outlined in the Method) during the first treatment excluding patients whose initial pressure was elevated or not known are tabulated in App. Tables II a, b, c, and d. (One table for each treatment for each race). A summary of the number of patients fulfilling one or more of the major criteria outlined in the definition of

* All tables designated "App. Table ---" are collected in a section called Appendix Tables.

TABLE XX

DISTRIBUTION OF PATIENTS ACCORDING TO THE NUMBER OF CYCLES COMPLETED ON THE FIRST TREATMENT FOR EACH RACE

	WHITE		INDIAN	
Cycles	Combined Tablet	IUD	Combined Tablet	IUD
1-5	84	26	18	8
6-10	63	14	11	5
> 10	146	13	40	5
Total	293	53	69	18

toxemia of pregnancy on one occasion or more than once during the cycle intervals considered, and in their whole treatment, is presented in Table XXI. Table XXIa excludes those patients whose initial blood pressure was elevated or was not known, Table XXIb shows this data for patients whose initial blood pressure was elevated, and Table XXIc for patients whose initial blood pressure was not known.

The distribution of patients who fulfilled the criteria for an elevated blood pressure at least once was not statistically different between the two treatments within each race. Significantly more ($P < 0.05$) white patients using the combined tablet had elevated blood pressures on more than one occasion during their whole treatment than did white patients using an IUD (Table XXIa). Forty-two of the 49 white patients using the combined tablet who had more than one elevated pressure reading over their whole course of treatment had completed more than 10 cycles, whereas neither of the two patients using an IUD in this group had been followed that long. More blood pressure readings were obtained in all patients who use the combined tablet because they had to return periodically to the Clinic for further supplies.

The percentage of patients in whom the interval from the lowest to the highest reading exceeded 30 mm. systolic and/or 15 mm. diastolic increased as the number of cycles followed (and therefore the number of pressure determinations) increased (App. Tables IIa-d). Similarly, the number of patients who met one or more of the criteria for an elevated blood pressure was higher in that part of the treatment after the tenth cycle (where more readings were generally taken) than in the other cycle groups which had fewer readings.

KEY TO TABLES XXIa, b, c

N - no. of patients in group

S - systolic blood pressure (mm. Hg)

D - diastolic blood pressure (mm. Hg)

* - numbers in brackets are percentage of the total patients on the treatment, e.g., in Table XXIa, of the 230 white patients using the combined tablet, 37 (16%) fulfilled criteria only once during their whole treatment, regardless of the length of treatment.

TABLE XXIa

SUMMARY OF NUMBER OF PATIENTS WITH "ELEVATED" BLOOD PRESSURES DURING THE FIRST TREATMENT BY CYCLE GROUPS AND FOR THE WHOLE TREATMENT FOR EACH TREATMENT AND RACE

a. Excluding Patients Whose Initial Blood Pressure Was Elevated or Not Known

CRITERIA: S ≧ 140 or D ≧ 90 or inc.S ≧ 30 or inc.D ≧ 15

	WHITE						INDIAN					
	Combined Tablet			IUD			Combined Tablet			IUD		
	N	Criteria reached: once	> once	N	Criteria reached: once	> once	N	Criteria reached: once	> once	N	Criteria reached: once	> once
In Whole Treatment												
Cycles Completed												
1-5	73	15	2	22	6	0	16	3	2	5	2	0
6-10	54	5	5	10	1	2	18	2	0	5	0	1
> 10	103	17	42	7	3	0	25	1	15	3	1	0
Total Patients	230	37 (16)*	49 (21)	39	10 (26)	2 (5)	49	6 (12)	17 (35)	13	3 (23)	1 (8)
By Cycle Groups												
Cycle Group												
1st 5 cycles	214	38	8	33	5	1	44	13	4	10	3	1
2nd 5 cycles	138	31	7	15	2	1	31	5	6	7	0	0
all cycles > 10	102	17	24	6	0	0	24	3	10	3	0	0

TABLE XXIb

SUMMARY OF NUMBER OF PATIENTS WITH "ELEVATED" BLOOD PRESSURES DURING THE FIRST TREATMENT BY CYCLE GROUPS AND FOR THE WHOLE TREATMENT FOR EACH TREATMENT AND RACE

b. Initial Blood Pressure Elevated

CRITERIA: S ≧ 140 or D ≧ 90 or inc.S ≧ 30 or inc.D ≧ 15

	WHITE						INDIAN					
	Combined Tablet			IUD			Combined Tablet			IUD		
	N	Criteria reached: once	Criteria reached: >once	N	Criteria reached: once	Criteria reached: >once	N	Criteria reached: once	Criteria reached: >once	N	Criteria reached: once	Criteria reached: >once
In Whole Treatment												
Cycles Completed												
1-5	7	2	3	3	0	1	1	0	0	2	0	0
6-10	6	1	3	2	1	0	2	1	0	0	0	0
> 10	19	4	11	5	1	2	9	1	8	1	0	1
Total Patients	32	7 (22)	17 (53)	10	2 (20)	3 (30)	12	2 (17)	8 (67)	3	0 (0)	1 (33)
By Cycle Groups												
Cycle Group												
1st 5 cycles	29	11	6	10	2	1	9	7	0	3	1	0
2nd 5 cycles	22	10	1	7	1	0	11	6	1	1	0	1
All cycles > 10	19	2	9	4	2	1	9	5	3	0	0	0

TABLE XXIc

SUMMARY OF NUMBER OF PATIENTS WITH "ELEVATED" BLOOD PRESSURES DURING THE FIRST TREATMENT BY CYCLE GROUPS AND FOR THE WHOLE TREATMENT FOR EACH TREATMENT AND RACE

c. Initial Blood Pressure Not Known

CRITERIA: S ≥ 140 or D ≥ 90 or inc.S ≥ 30 or inc.D ≥ 15

	WHITE						INDIAN					
	Combined Tablet			IUD			Combined Tablet			IUD		
	N	Criteria reached: once	Criteria reached: > once	N	Criteria reached: once	Criteria reached: > once	N	Criteria reached: once	Criteria reached: > once	N	Criteria reached: once	Criteria reached: > once
In Whole Treatment												
Cycles Completed												
1-5	4	2	0	1	0	0	1	0	0	1	0	1
6-10	3	2	1	2	0	1	1	0	0	0	0	0
> 10	24	5	8	1	1	0	6	4	2	1	0	0
Total Patients	31	9	9	4	1	1	8	4	2	2	0	1
		(29)	(29)		(25)	(25)		(50)	(25)		(0)	(50)
By Cycle Groups												
Cycle Group												
1st 5 cycles	10	3	0	2	1	0	3	1	0	2	0	1
2nd 5 cycles	19	4	1	3	1	0	4	1	0	0	0	0
all cycles > 10	23	6	8	1	1	0	6	4	2	1	0	0

When the comparison between treatments was limited to the first 10 cycles for patients who had completed at least 10 cycles, there was no statistically significant difference between the proportions of patients in each treatment group who met the chosen criteria for elevation of blood pressure as the following table demonstrates:

ANALYSIS OF THE NUMBER OF WHITE PATIENTS WITH BLOOD PRESSURE ELEVATIONS DURING THE FIRST 10 CYCLES OF TREATMENT:

TREATMENT	COMBINED TABLET	IUD
A. Initial blood Pressure Normal		
Numbers of patients completing at least 10 cycles:	129	9
Blood Pressure Elevated		
- once during lst 10 cycles	25	1
- more than once	26	1
B. Initial Blood Pressure Elevated		
Numbers of patients completing at least 10 cycles:	20	6
Blood Pressure Elevated		
- once during lst 10 cycles	4	1
- more than once	9	3

Significantly more Indian patients than white patients using the combined tablet fulfilled these criteria more than once during their whole treatment ($P < 0.05$) (Table XXIa). A slightly higher percentage of the Indian patients in this category had completed more than 10 cycles on the combined tablet than had the white patients.

Figs. Ia and Ib show the proportion of patients in each treatment group who fulfilled one of the major criteria on at least one occasion in each of the three cycle groupings. Only those patients in whom blood pressure was recorded in each of the cycle groupings were included in this figure. Patients whose initial pressure was elevated and those whose initial pressure was not known are depicted separately. Where the groups of patients who had completed more than ten cycles were large enough to analyze, there was no significant difference within each treatment in the proportions who had fulfilled the criteria in each of these three cycle groupings and those who had not in any of the three cycle groupings. At least half of the white patients had variable elevations in blood pressure: it was elevated in one or more of the cycle groupings but not in the others. The proportions of patients in each treatment group within each race who met one or more of the major criteria on at least one occasion in each of their cycle groups were not significantly different. There was no significant difference between white and Indian patients using the IUD but a higher percentage of Indian patients than white patients who used the combined tablet met these criteria in all cycle groupings ($P < 0.001$).

Figures 2a and b show the percentage distribution of the changes in weight percentile from the initial weight percentile during the first contraceptive treatment

KEY TO FIGURES 1a and 1b

The three vertical columns of blocks represent the lengths of time that the various groups of patients were followed. The figures are the actual numbers of patients in each group and the subdivisions of the blocks are proportional to the magnitude of these numbers. All shaded areas represent elevation of blood pressure. Horizontal shading represents initial blood pressure elevation or elevation in all cycle groupings during which the patient was followed. The other shadings indicate sporadic blood pressure elevations. Clear areas represent no elevation of blood pressure initially or during treatment. For example, in the top right-hand block in Figure 1a, 16 white patients using the combined tablet who had an initially elevated blood pressure were followed longer than 10 cycles. In the third cycle grouping, it can be seen that four patients had no elevated readings throughout their treatment, three remained elevated throughout, and nine varied.

Fig. 1a - WHITE

TIME TREND - BLOOD PRESSURE ELEVATION

COMBINED TABLET

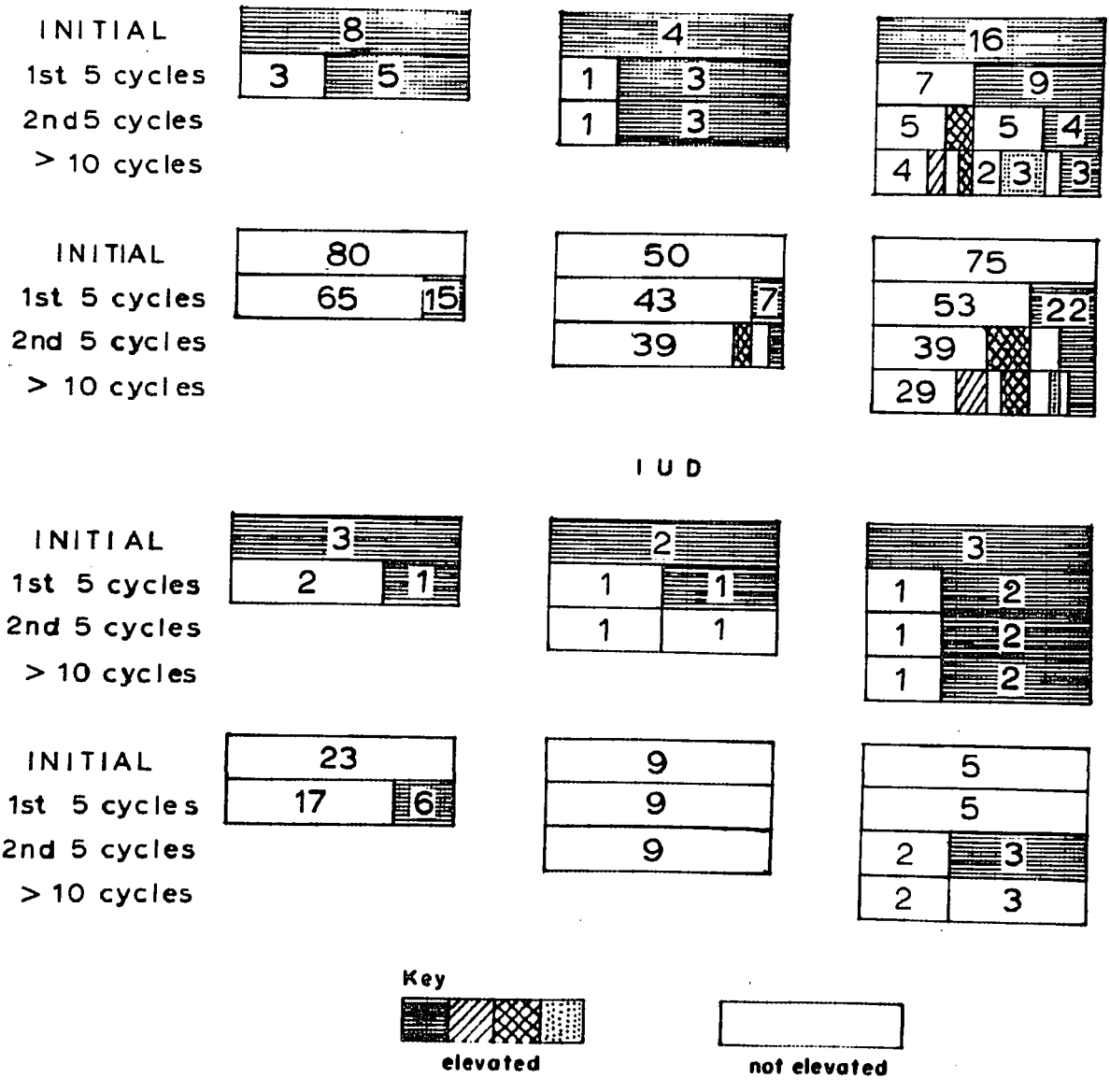


Fig. 1b - INDIAN

TIME TREND - BLOOD PRESSURE ELEVATION

COMBINED TABLET

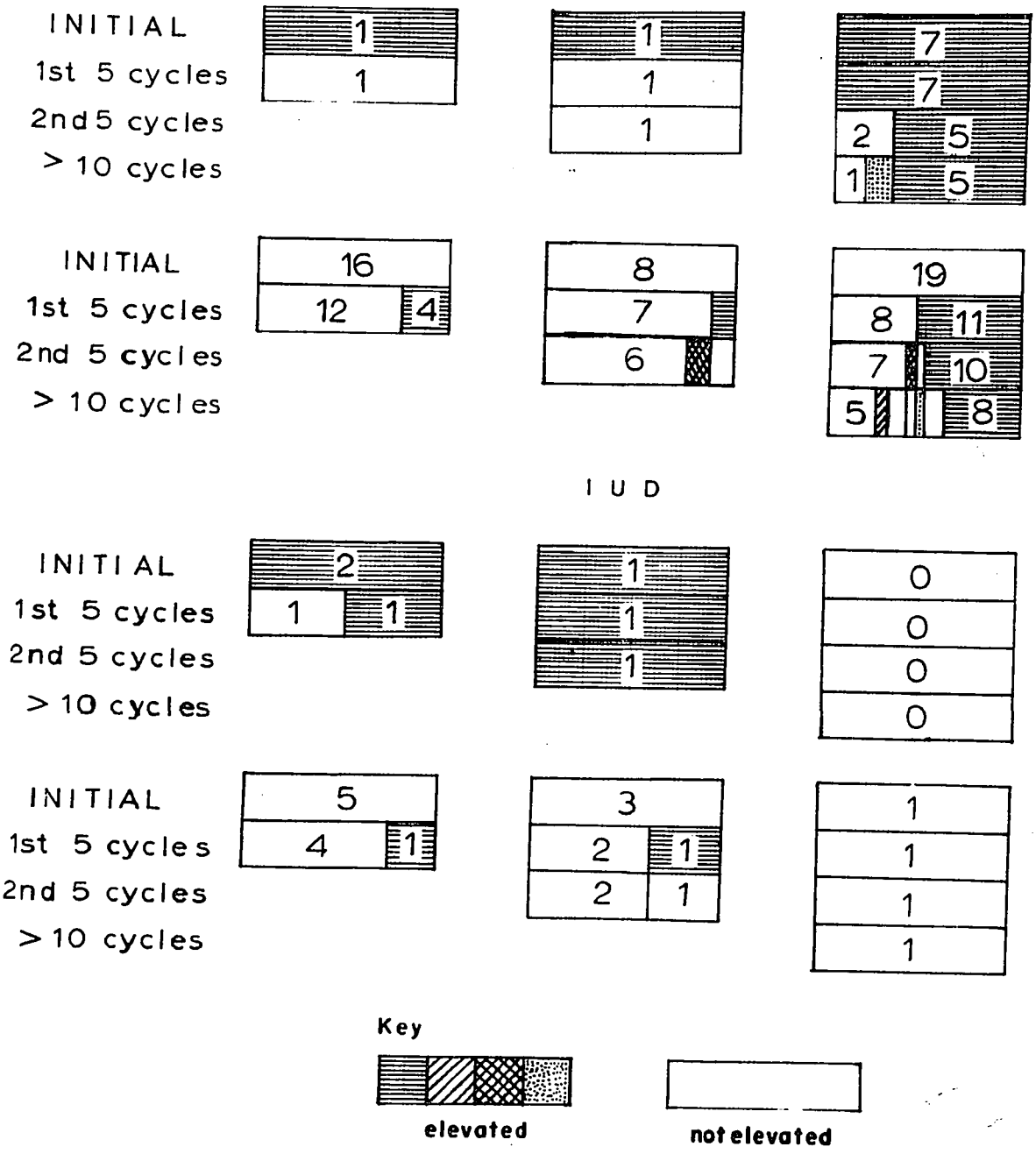


Fig. 2A - WHITE
PERCENTAGE DISTRIBUTION OF CHANGES IN WEIGHT PERCENTILE
DURING FIRST TREATMENT

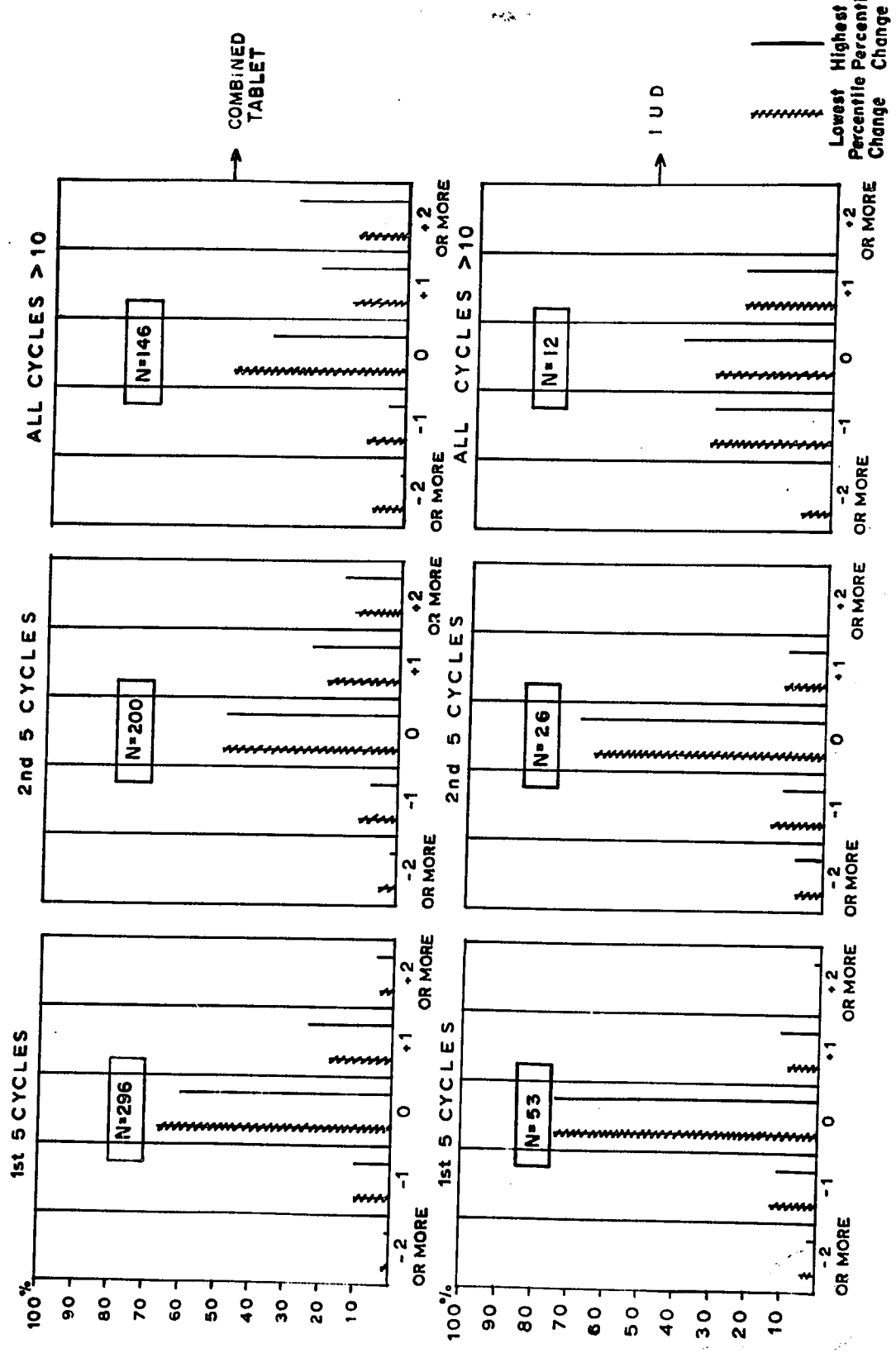
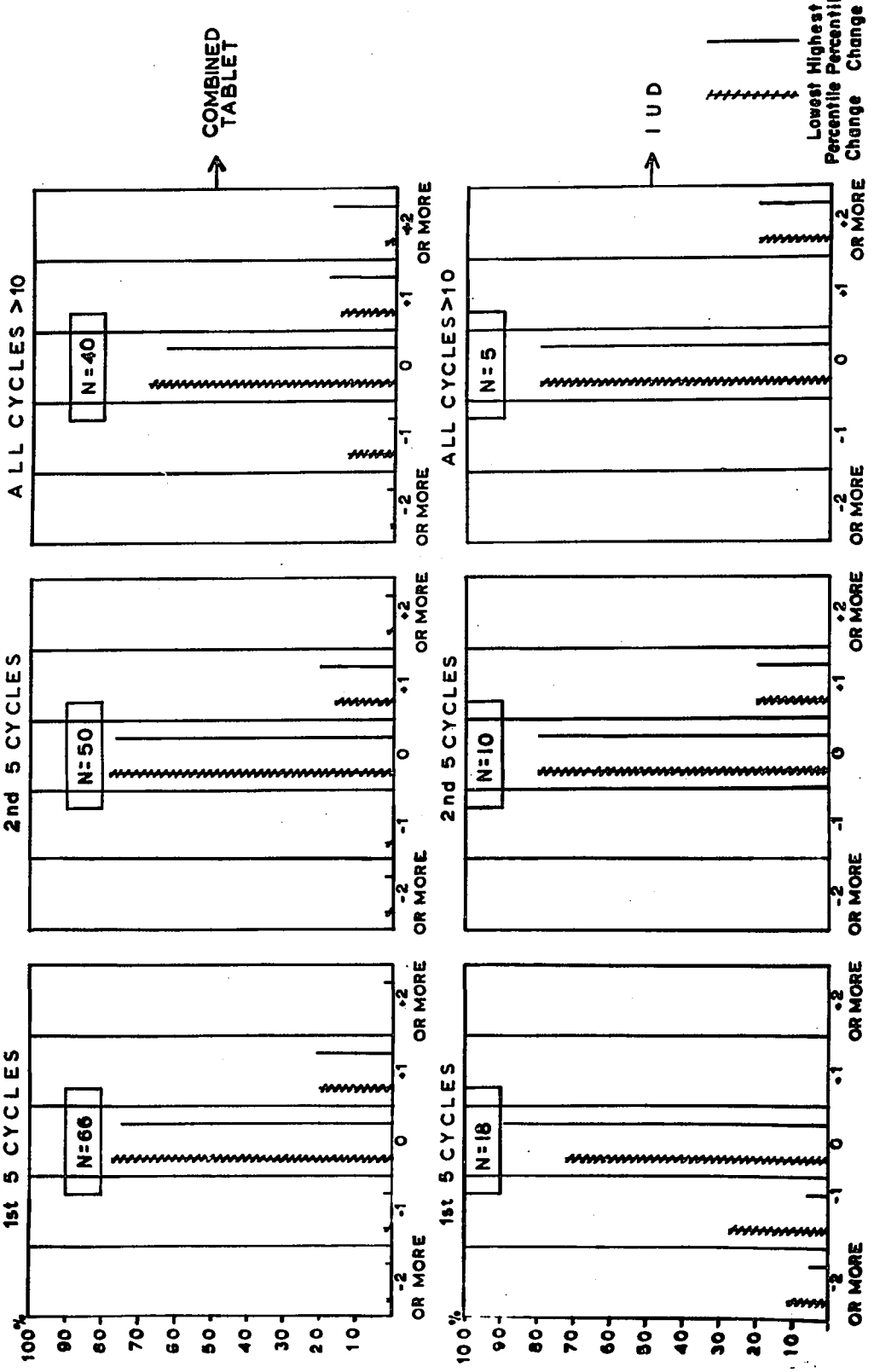


Fig.2B INDIAN

PERCENTAGE DISTRIBUTION OF CHANGES IN WEIGHT
PERCENTILE DURING FIRST TREATMENT



according to the treatment and for each of the three cycle groups considered. The figures show that more patients using the combined tablet than using an IUD had a positive change. However, some of the patients had a negative change in weight percentile, e.g., in white patients using the combined tablet, the highest weight recorded in the first five cycles was enough less than the initial weight to move 10 percent into the next lower weight percentile category, and one percent moved even lower. In white patients using an IUD, the highest weight recorded was enough less than the initial to move 11 percent into the next lower weight percentile category and two percent even lower. Although these figures illustrate the changes in weight, they are not completely accurate because in patients whose initial weight percentile category was much greater than the 75th, increases and some decreases in weight would not be reflected accurately. Similarly, in patients whose initial weight percentile category was much less than the 25th percentile for their age group, weight losses and some gains would not be reflected accurately.

Because this was not an accurate method for assessing changes in those patients at the two extremes of the weight range, a clearer picture of weight changes during treatment can be obtained from the weight scores as described in the Method and utilized in Chapter V. From Tables XXIX a and b (part 1), the following table is derived:

PERCENTAGE DISTRIBUTION OF WEIGHT PERCENTILE CHANGES OBTAINED FROM MAXIMUM WEIGHTS RECORDED DURING THE ENTIRE FIRST TREATMENT

	% OF WHITE PATIENTS		% OF INDIAN PATIENTS	
	Combined tablet N = 266	IUD N = 46	Combined tablet N = 65	IUD N = 22
Weight Change				
0*	39	61	38	36
1**	37	24	38	41
2***	24	15	24	23

* weight gain was insufficient to move to the next higher percentile category or a negative weight change occurred

** weight increased sufficiently to move to the next higher percentile category for that age group

*** weight increased sufficiently to move to the second or higher percentile category above the initial level

Fewer of the white patients who used an IUD moved into a higher weight percentile category during their whole first treatment than either white patients who used the combined tablet or Indian patients who used either type of treatment. The above table shows that the distributions of the weight changes among the patients are almost identical in these latter three groups.

Mean weight changes in pounds were calculated for each treatment for

each cycle group. The distribution of the mean highest and lowest weights recorded during each cycle grouping expressed as a change from the initial weight according to the initial ratio of the weight percentile to the height percentile is tabulated in Appendix Tables Va, b, c, and d. In none of the treatments was there any particular trend related to the initial ratio.

In Table XXII, a summary of the mean maximal weight changes is presented by cycle grouping for each treatment. In both the white and Indian patients using the combined tablet and the Indian patients using an IUD the mean maximal weight change was always positive and it increased as the length of the treatment progressed. In patients of both races using the combined tablet, these mean changes were highly significant for each cycle grouping ($P < 0.001$). In the Indian patients using an IUD, the mean change in the second five cycles was not significant but in the other two cycle groupings, the P value was less than 0.01. In the white patients using an IUD, the mean maximal weight change in the first five cycles was positive ($P < 0.05$). The mean weight change in the second five cycles, although not as high, was still positive but was not significant. In the third time period, the mean maximal weight change was negative but also was not significant. In most treatment groups, the standard deviation was larger than the mean maximal weight change from the initial weight, showing that a number of patients within each group actually did lose weight.

TABLE XXII

SUMMARY OF THE MEAN MAXIMUM WEIGHT CHANGES* DURING THE FIRST TREATMENT

BY CYCLE GROUP FOR EACH TREATMENT AND RACE

Cycle Group	WHITE $\bar{X}$	S.D.	S.E.M.	N	P	INDIAN $\bar{X}$	S.D.	S.E.M.	N	P
					Combined Tablet					
1st 5	+2.4	± 5.33	± 0.310	296	< 0.001	+3.9	± 4.25	± 0.531	64	< 0.001
2nd 5	+4.6	± 8.27	± 0.576	206	< 0.001	+5.1	± 6.07	± 0.867	49	< 0.001
> 10	+8.9	± 11.75	± 0.963	149	< 0.001	+12.4	± 8.48	± 1.376	38	< 0.001
					IUD					
1st 5	+2.1	± 6.64	± 0.903	54	< 0.05	+4.3	± 6.42	± 1.473	19	< 0.01
2nd 5	+1.6	± 9.30	± 1.757	28	> 0.3	+6.8	± 11.76	± 3.720	10	> 0.1
> 10	-3.3	± 10.26	± 2.963	12	> 0.2	+14.8	± 6.69	± 2.990	5	< 0.01

$\bar{X} \pm$ S.D. $\pm$ S.E.M. - Mean $\pm$ Standard Deviation $\pm$ Standard Error of the Mean

N - number in group

P - probability that the weight change is significantly different from the initial value

* mean maximum weight changes in lb.

CHAPTER IV: CHANGES IN BLOOD PRESSURE AND WEIGHT DURING THE FIRST VIABLE PREGNANCY.

The emphasis in this chapter is on the changes in blood pressure and weight during the first viable pregnancy, although comparisons have been made between the performances of white and Indian patients.

Table XXIII shows the percentage age distribution of the patients at the start of the first viable pregnancy according to the time of their first visit to the hospital physicians. From the total columns for each race, it can be seen that at the time of their first viable pregnancy a slightly higher proportion of Indian patients than white were under the age of 16 and, in general, the Indian patients tended to be younger than the white at that time. At least three-fifths of the patients of each race were under 20 years of age and, thus, for further consideration, the age was divided into those under 20 and those 20 and over. Because the definition of toxemia of pregnancy outlined by the American Committee on Maternal Welfare (Eastman and Hellman, 1965) specifies that hypertension discovered in pregnancy before the 24th week of gestation may indicate chronic hypertensive vascular disease, the time the patient first visited a hospital physician during the first viable pregnancy was noted. Twenty weeks was considered a convenient division for the purposes of this study and was the time chosen by MacGillivray (1961) and others for purposes of comparison. Patients with no prenatal record did

TABLE XXIII

PERCENTAGE AGE DISTRIBUTION OF CLINIC PATIENTS AT THE BEGINNING OF THE FIRST VIABLE PREGNANCY ACCORDING TO THE TIME OF THE FIRST VISIT TO THE HOSPITAL PHYSICIANS FOR EACH RACE

Age (years)	WHITE (N=498) First Visit < 20 wk. N=42	First Visit >20 wk. N=67	No Prenatal Record N=389	Total N=498	INDIAN (N=112) First Visit <20 wk. N=23	First Visit >20 wk. N=53	No Prenatal Record N=36	Total N=112
<16	2	9	4	5	17	2	17	10
16-17	48	42	20	25	48	43	33	41
18-19	31	30	31	31	26	32	11	23
20-24	12	19	25	23	9	21	28	21
25-29	5	0	3	3	0	2	3	2
30-34	2	0	0	0	0	0	3	1
not known	0	0	17	13	0	0	5	2

N - no. in group

not necessarily go without prenatal care but may have attended a private physician or a physician on the Indian Reserve instead of the hospital Clinic.

The incidence of "preeclampsia" or "eclampsia" noted from diagnoses on available clinic and hospital charts was 17 percent in the white patients and 28 percent in the Indian patients.

Table XXIV summarizes the percentage distribution of blood pressure changes for each race during the first viable pregnancy excluding those patients who had an elevated initial reading. Because further divisions of blood pressure levels are included in classifying the preeclampsia as severe or mild, the highest reading after 20 weeks gestation for each patient was included. The data for this table were derived from the "total" columns of App. Tables III and IV. A higher proportion of Indian than white patients fulfilled one or more of the four major criteria (outlined in the Method) on at least one occasion (white patients, 68 percent; Indian patients, 85 percent - $P < 0.001$). When only those patients who fulfilled the criteria on more than one occasion at least six hours apart (white patients, 52 percent; Indian patients, 64 percent) were compared, the difference was not significant although, again, the percentage of Indian patients in this category was somewhat higher than that of the white patients. Similarly, when only those patients were considered whose initial blood pressure was elevated (App. Tables IVa and b), there were no significant differences in the distribution of Chi Square between the white and Indian patients for an elevation of blood pressure on at least one occasion, or on more than one occasion. At least one-quarter of all patients in these tables never had elevated blood pressures recorded after the initial elevated reading.

TABLE XXIV

PERCENTAGE DISTRIBUTION OF BLOOD PRESSURE CHANGES DURING THE FIRST VIABLE PREGNANCY BY RACE EXCLUDING PATIENTS WITH AN ELEVATED INITIAL READING

Criteria	WHITE %	WHITE N	INDIAN %	INDIAN N
After Initial				
S ≧ 140 once	14	170	20	79
S ≧ 140 > once	15	170	29	79
D ≧ 90 once	16	170	20	79
D ≧ 90 > once	32	170	34	79
S ≧ 140 and D ≧ 90	15	170	46	79
Elevation From Initial				
S ≧ 30 once	11	149	13	77
S ≧ 30 > once	8	149	21	77
D ≧ 15 once	11	149	19	77
D ≧ 15 > once	41	149	8	77
S ≧ 30 and D ≧ 15	11	149	31	77
S ≧ 140 or D ≧ 90 or inc.			S ≧ 30 or inc. D ≧ 15	
once	16	170	21	79
> once	52	149	64	77
Lowest To Highest Reading				
S > 30	40	149	48	77
D > 15	77	149	86	77
S > 30 and D > 15	27	149	48	77
Highest Reading After 20 Weeks				
S — 140-159	25	170	38	79
S = 160	6	170	14	79
D — 90-109	42	170	57	79
D = 109	6	170	10	79

N - no. in group
S - systolic blood pressure (mm.Hg)
D - diastolic blood pressure (mm.Hg)

Table XXV shows the percentage distribution of the ratio of the weight percentile to the height percentile at the beginning of the first viable pregnancy for patients in the age groups under 20, and 20 and over. The total numbers in this table for each group are smaller than in App. Tables IIIa and b. The reason for this is that blood pressures were routinely measured during hospital admission but in the many cases who did not attend the Prenatal Clinic, the weight was not known and some of these were obtained subsequently by questioning.

In patients whose initial ratio of weight percentile to height percentile was known, no significant difference was found in the distribution of the three ratios among patients in the two age groups in either race. There was a difference when the total patients of the two races were compared as to the distribution of these ratios ($P < 0.05$), contributed mostly by the higher percentage of Indian patients with a ratio greater than 1 and a lower percentage with a ratio equal to 1.

Table XXVI shows the percentage distribution of the maximal weight gain during the first viable pregnancy for patients under 20 years of age and 20 and over. The figure for the maximal weight gain during this pregnancy was obtained from the prenatal records, where they were available, or from the patient's statement of her maximal weight gain at the time of delivery. No differences were found in the distribution of the maximal weight gains according to the intervals outlined in Table XXVI between these two age groups except in the white patients where the difference approached significance mainly because of the higher proportion of older women with a total gain of less than 20 pounds and a lower proportion in this age group with a gain of 20 to 24 pounds.

In Figure 3, the percentage distribution of the maximal weight gain during

TABLE XXV

PERCENTAGE DISTRIBUTION OF THE RATIO OF THE WEIGHT PERCENTILE TO THE HEIGHT PERCENTILE AT THE BEGINNING OF THE FIRST VIABLE PREGNANCY FOR EACH AGE GROUP AND RACE

	WHITE (N=183)			INDIAN (N=77)		
	AGE (Years)					
Ratio	<20 N=144	≥20 N=39	Total N=183	<20 N=61	≥20 N=16	Total N=77
< 1	42	44	43	34	56	39
1	20	20	20	12	6	10
> 1	29	28	28	49	32	46
Not Known	9	8	9	5	6	5

N - no. in group

Ratio - weight percentile:height percentile

TABLE XXVI

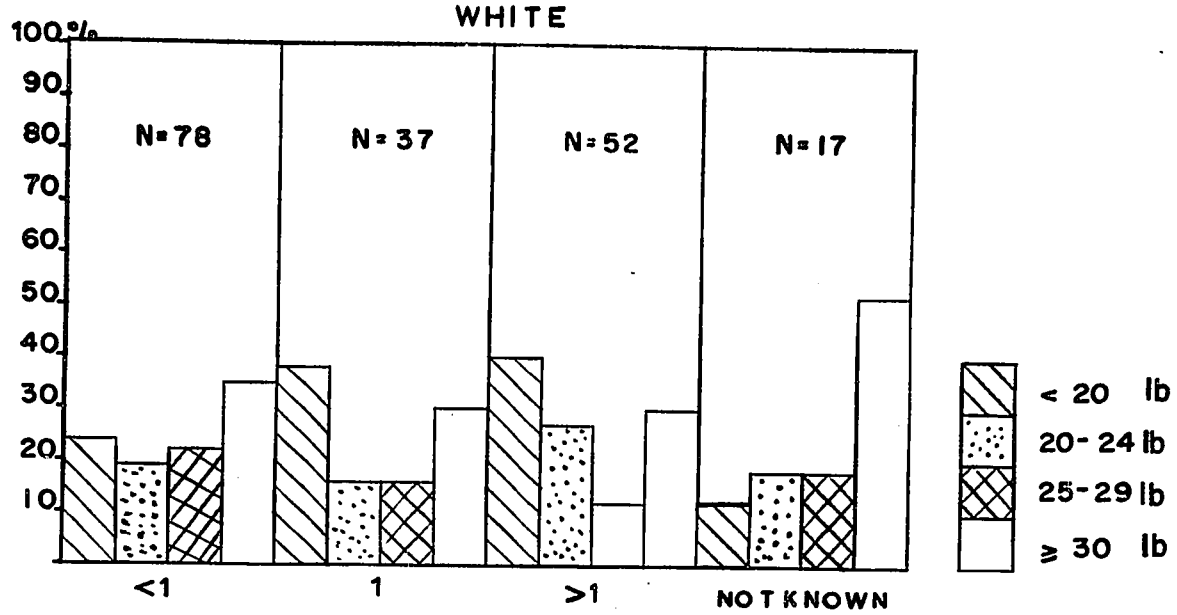
PERCENTAGE DISTRIBUTION OF THE MAXIMUM WEIGHT GAIN DURING THE FIRST VIABLE PREGNANCY FOR EACH AGE GROUP AND RACE

Maximum Gain (lb.)	WHITE AGE (Years) <20 N=144	WHITE AGE (Years) ≥20 N=39	WHITE Total N=183	INDIAN AGE (Years) <20 N=61	INDIAN AGE (Years) ≥20 N=16	INDIAN Total N=77
< 20	27	43	31	34	31	34
20-24	21	8	18	26	19	25
25-29	16	23	17	10	25	13
≥ 30	36	26	34	30	25	28

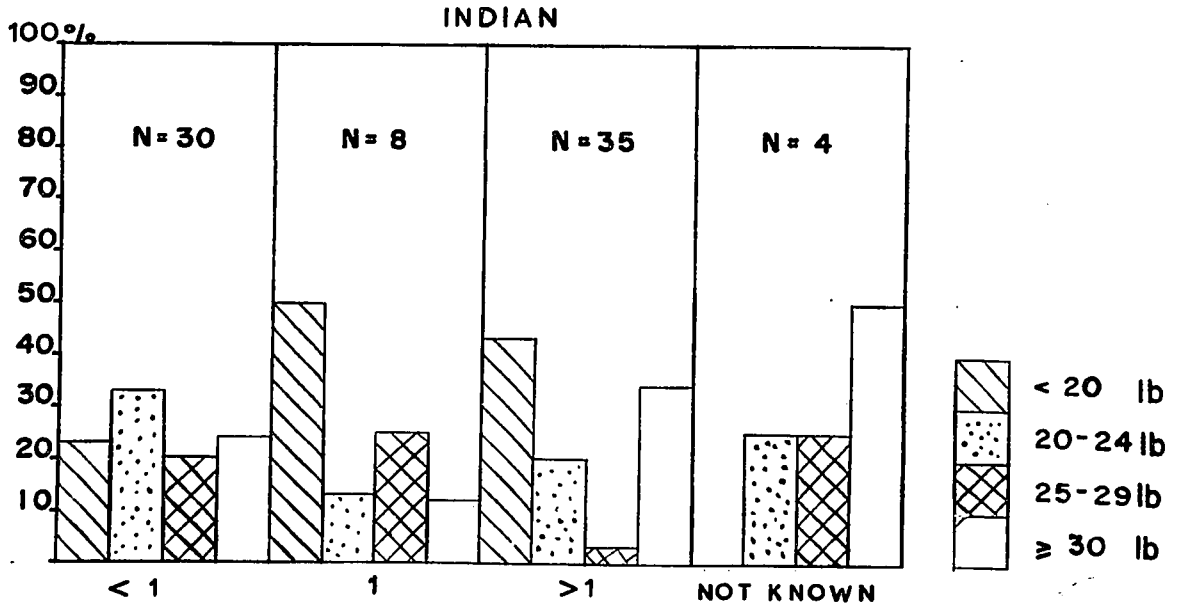
N - no. in group

Fig. 3

PERCENTAGE DISTRIBUTION OF WEIGHT GAINS
DURING FIRST VIABLE PREGNANCY



WEIGHT PERCENTILE: HEIGHT PERCENTILE



WEIGHT PERCENTILE: HEIGHT PERCENTILE

the first viable pregnancy for patients of each ratio of weight percentile to height percentile at the beginning of that pregnancy is depicted. There were no differences in the distribution of the maximal weight gain for the different ratios.

In Figure 4, the percentage distribution of weight gains between prenatal visits during the first viable pregnancy is depicted. The weight gains chosen for these intervals were considered a possible reflection of water retention, particularly when they occurred in the last trimester. During the first six months of pregnancy, patients customarily attend the Clinic at monthly intervals; during the next two months they usually attend every two weeks; whereas in the last month of gestation, visits are weekly. Visits are also weekly, or even more frequent, if there are problems involved, particularly excessive weight gain, edema or blood pressure elevation. No differences existed in the distribution of the frequency of the interval weight gains specified except for a higher proportion of Indian than white patients who had never gained at least 1.5 pounds in any one week ($P < 0.05$).

In Table XXVII, the percentage distribution of the weight gains between prenatal visits to the hospital Clinic during the first viable pregnancy is tabulated according to the maximal weight gain for that pregnancy. From inspection of the table, it can be seen that the percentage of white patients with none of these interval weight gains decreased as the maximal weight gain increased. No such trend existed in the Indian patients. When patients were grouped according to their maximal weight gains, the distribution of those who had none of the interval weight gains was significant in the white patients ($P < 0.05$). More white patients than expected who had a maximal weight gain of less than 20 pounds had none of the interval gains, and fewer white patients than expected with a maximal gain of 30 or more pounds had

Fig. 4

PERCENTAGE DISTRIBUTION OF INTERVAL WEIGHT GAINS IN FIRST VIABLE PREGNANCY

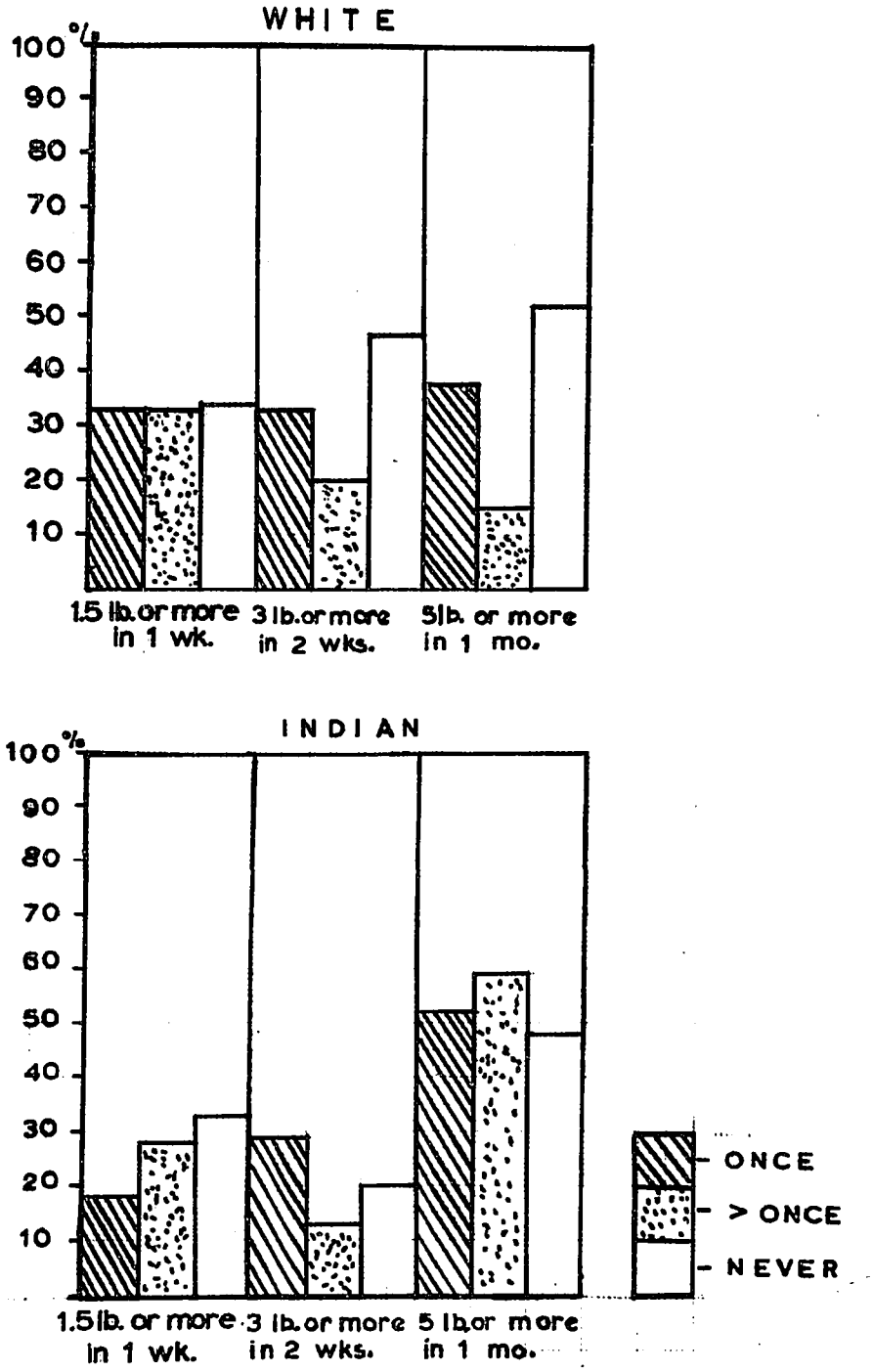


TABLE XXVII

PERCENTAGE DISTRIBUTION OF WEIGHT GAINS OF CLINIC PATIENTS BETWEEN PRENATAL VISITS DURING THE FIRST VIABLE PREGNANCY ACCORDING TO THE MAXIMUM WEIGHT GAIN FOR EACH RACE

Interval Gain (lb.)	WHITE (N=87) MAXIMUM WEIGHT GAIN (lb.)					INDIAN (N=38) MAXIMUM WEIGHT GAIN (lb.)				
	< 20 N=22	20-24 N=16	25-29 N=18	≧ 30 N=31	Total N=87	< 20 N=10	20-24 N=11	25-29 N=6	≧ 30 N=11	Total N=38
1. only ≧ 1½ in 1 wk.	23	13	5	10	13	30	18	0	0	13
2. only ≧ 3 in 2 wk.	9	0	17	10	9	30	9	0	9	13
3. only ≧ 5 in 1 mo.	0	19	5	5	7	20	28	0	9	16
Combination 1 + 2	9	12	17	23	16	10	9	0	18	11
1 + 3	18	6	17	23	17	10	9	33	28	18
2 + 3	14	6	5	6	8	0	9	17	18	11
1 + 2 + 3	4	25	28	23	20	0	0	17	9	5
none of above	23	19	6	0	10	0	18	33	9	13

N - no. in group

none of the interval gains. Between the total white and total Indian patients, the difference approached significance. A somewhat higher proportion of Indian patients than expected who had a maximal gain of 25 pounds or more had none of the interval gains.

In Table XXVIII, the percentage distribution of the largest weight gain in any one-week interval during the first viable pregnancy is tabulated. From inspection of the table, it can be seen that approximately 50 percent of the patients gained three pounds or more in a one-week interval.

The mean maximal weight gain during the first viable pregnancy was calculated for each initial ratio of the weight percentile to the height percentile for each age group in each race. There were no significant differences between these means and none of these mean weight gains was significantly different from an average of 24 pounds. The mean maximal weight gain for the whole white group, where weights were available, was 25.0 pounds with a standard deviation of 10.45. The mean maximal weight gain for the Indian patients was 24.4 pounds with a standard deviation of 10.74. There was no significant difference between these means.

TABLE XXVIII

PERCENTAGE DISTRIBUTION OF THE LARGEST WEIGHT GAIN IN ANY ONE-WEEK INTERVAL DURING THE FIRST VIABLE PREGNANCY FOR EACH RACE

Weight Gain (lb.)	WHITE N=90	INDIAN N=42
< 1	10	9
1	1	17
2	39	29
3	15	19
4	21	17
5	14	9

N - no. in group

CHAPTER V: SCORING OF BLOOD PRESSURE AND WEIGHT CHANGES OCCURRING DURING CONTRACEPTIVE TREATMENT AND IN PREGNANCY.

All tables in this chapter show the scores for changes in blood pressure and/or weight during one or more treatments and/or during pregnancy. Numbers lying along the diagonal line represent the number of patients whose score was the same for both parameters (blood pressure and weight) or whose score for one parameter was the same in the two situations (e.g., treatment and pregnancy). For a perfect correlation of scores, all numbers would be on the diagonal line, but in all of the tables, there is a considerable deviation from this pattern.

Tables XXIXa and b (part I) show the comparison of blood pressure and weight scores for each treatment. McNemar's modification of the Chi Square test revealed that the proportion of white patients who, during either treatment, had elevated blood pressures (i.e., scores of 1 or 2) was not different from the proportion who gained weight during treatment (i.e., scores of 1 or 2). For example, in Table XXIXa (part I) in which the scores for the white patients using the combined tablet are compared, the number who had scores of 1 or 2 for blood pressure change (47+11+62+14+36+7 = 177) as a proportion of the total $\left(\frac{177}{177+46+22+21}\right)$ is not significantly different from the proportion $\frac{(22+21+62+36+14+7)}{266}$ who had scores of 1 or 2 for weight changes. Significantly more of the Indian patients

KEY TO TABLES XXIXa AND XXIXb

Numbers lying along the diagonal line represent the number of patients whose score was the same for both parameters (blood pressure and weight) or whose score for one parameter was the same in the two situations (treatment and pregnancy). For example, in Part 1 of Table XXIXa, 46 white patients who used the combined tablet had a blood pressure score of 0 and a weight score of 0 during this treatment. For a perfect correlation of scores, all numbers would be on the diagonal line.

TABLE XXIXa

COMPARISON OF BLOOD PRESSURE AND WEIGHT SCORES

Number of White Patients

Combined Tablet

IUD

Part 1. Blood Pressure Vs. Weight During Treatment

Wt. Score	B.P. Score 0	B.P. Score 1	B.P. Score 2
0	46	47	11
1	22	62	14
2	21	36	7

Wt. Score	B.P. Score 0	B.P. Score 1	B.P. Score 2
0	17	11	0
1	4	6	1
2	2	4	1

Part 2. Blood Pressure Vs. Weight During Pregnancy

Wt. Score	B.P. Score 0	B.P. Score 1	B.P. Score 2
0	7	29	11
1	9	60	52
2	2	41	43

Wt. Score	B.P. Score 0	B.P. Score 1	B.P. Score 2
0	0	5	2
1	0	13	7
2	0	9	7

Part 3. Blood Pressure During Treatment Vs. Blood Pressure During Pregnancy

Preg. Score	Treatment Score 0	Treatment Score 1	Treatment Score 2
0	8	8	3
1	42	71	50
2	3	14	17

Preg. Score	Treatment Score 0	Treatment Score 1	Treatment Score 2
0	0	0	0
1	12	15	1
2	8	8	2

Part 4. Weight During Treatment Vs. Weight During Pregnancy

Preg. Score	Treatment Score 0	Treatment Score 1	Treatment Score 2
0	23	11	6
1	38	54	27
2	44	34	11

Preg. Score	Treatment Score 0	Treatment Score 1	Treatment Score 2
0	6	2	0
1	14	5	3
2	8	5	4

TABLE XXIXb

COMPARISON OF BLOOD PRESSURE AND WEIGHT SCORES

Number of Indian Patients

Combined Tablet

Part 1. Blood Pressure Vs. Weight During Treatment

Wt. Score \ B.P. Score	0	1	2
0	10	9	6
1	4	15	6
2	1	6	8

Part 2. Blood Pressure Vs. Weight During Pregnancy

Wt. Score \ B.P. Score	0	1	2
0	1	4	8
1	0	7	20
2	0	6	20

Part 3. Blood Pressure During Treatment Vs. Blood Pressure During Pregnancy

Preg. Score \ Treatment Score	0	1	2
0	0	2	0
1	2	11	3
2	15	17	17

Part 4. Weight During Treatment Vs. Weight During Pregnancy

Preg. Score \ Treatment Score	0	1	2
0	9	5	0
1	8	13	8
2	9	8	7

IUD

Part 1. Blood Pressure Vs. Weight During Treatment

Wt. Score \ B.P. Score	0	1	2
0	6	2	0
1	8	0	1
2	4	1	0

Part 2. Blood Pressure Vs. Weight During Pregnancy

Wt. Score \ B.P. Score	0	1	2
0	0	2	1
1	0	1	5
2	0	2	12

Part 3. Blood Pressure During Treatment Vs. Blood Pressure During Pregnancy

Preg. Score \ Treatment Score	0	1	2
0	0	0	0
1	5	0	0
2	9	6	2

Part 4. Weight During Treatment Vs. Weight During Pregnancy

Preg. Score \ Treatment Score	0	1	2
0	0	1	0
1	2	3	1
2	9	4	3

using the combined tablet had a score of 1 or 2 for blood pressure than for weight ($P < 0.05$) but in the Indian patients using an IUD, a higher proportion had these scores for weight than for blood pressure ($P < 0.02$). In the Indian patients, the difference in the distribution of patients with identical scores for blood pressure and weight during treatment approached significance because a lower proportion of patients using an IUD than of those using the combined tablet had identical scores. Fewer Indian than white patients using an IUD tended to have identical blood pressure and weight scores during treatment. No other significant differences were found.

The same comparison of scores (Tables XXIXa and b) (part 2) during pregnancies preceding the first treatment showed that among patients of each race who used the combined tablet, a higher proportion had a score of 1 or 2 for blood pressure than for weight ($P < 0.001$). This analysis could not be performed for either of the groups of patients who used an IUD; there were too few patients. There were no differences in the proportions of patients later using the two different treatments who had identical scores for both parameters during pregnancy. Nor were there any differences in the proportions of white and Indian patients who later used the same treatment.

Tables XXIXa and b (parts 3 and 4) compare the scores for the whole of the first treatment and for all pregnancies occurring before that treatment. Significantly more of the white patients had blood pressure scores of 1 or 2 during pregnancy ($P < 0.001$) than during either treatment and more had weight scores of 1 or 2 during pregnancy than during treatment with the combined tablet ($P < 0.05$) or with an IUD ($P < 0.001$). Significantly more of the Indian patients had blood pressure

scores of 1 or 2 during pregnancy than during use of the combined tablet ($P < 0.01$) or with an IUD ($P < 0.001$). Also when the weight scores were considered, they were higher during pregnancy, than during treatment (combined tablet, $P < 0.02$; IUD, $P < 0.01$). A significantly lower proportion of Indian patients using an IUD than of those using the combined tablet had identical blood pressure scores during treatment and in pregnancy ($P < 0.01$). Similarly, the only difference between Indian and white patients using the same treatment was due to the significantly lower proportion of Indian than white patients using an IUD who had identical blood pressure scores ($P < 0.05$).

Table XXX compares the combined score (blood pressure and weight scores - see Method) during treatment and during pregnancy. A significantly larger proportion of patients had high combined scores (4, 5, or 6) during pregnancy than during treatment, regardless of the type of treatment ($P < 0.001$ for all treatment groups except the Indian patients using the combined tablet where $P < 0.01$). No significant differences either between treatment groups or between patients of the two races using the same treatment were found in the proportion of each group with identical combined scores in pregnancy and during treatment.

In Table XXXI, the comparison of blood pressure and weight scores during two separate treatments for the same patient is presented for white patients. The small number of Indian patients with two treatments did not warrant analysis. For patients with two non-consecutive treatments using the combined tablet (Part A), approximately the same proportion scored 1 or 2 both times that they used the combined tablet when each parameter was considered separately. Statistical analysis could not be performed. For patients who changed directly from the com-

KEY TO TABLE XXX

Numbers lying along the diagonal line represent the number of patients whose combined score was the same during treatment as it was during pregnancy. For example, 15 white patients had a combined score of 2 during treatment with the combined tablet and a combined score of 2 during their pregnancies preceding that treatment. For a perfect correlation of combined scores, all numbers would be on the diagonal line.

TABLE XXX

COMBINED SCORES *FOR BLOOD PRESSURE AND WEIGHT CHANGES DURING TREATMENTS AND DURING PREGNANCY

Number of White Patients

Comb. Tab. Score \ Pregnancy Score	1	2	3	4	5	6
1	2	6	3	5	20	10
2	2	15	4	16	19	13
3	1	3	2	4	7	3
4	1	4	2	19	27	9
5	1	10	1	16	16	6
6	0	0	1	0	4	2

IUD Score \ Pregnancy Score	1	2	3	4	5	6
1	0	3	0	4	4	1
2	0	1	2	7	6	2
3	0	0	0	0	0	1
4	0	1	0	2	1	2
5	0	0	0	0	5	0
6	0	0	0	0	0	1

Number of Indian Patients

Comb. Tab. Score \ Pregnancy Score	1	2	3	4	5	6
1	0	0	4	1	2	3
2	1	2	0	1	3	6
3	0	0	1	0	3	3
4	0	2	1	4	6	2
5	0	0	2	1	4	2
6	0	0	0	0	4	4

IUD Score \ Pregnancy Score	1	2	3	4	5	6
1	0	0	1	0	2	4
2	0	2	0	0	4	4
3	0	0	0	1	1	2
4	0	0	0	0	0	0
5	0	0	0	0	0	2
6	0	0	0	0	0	0

* For explanation of how combined score was calculated see Method.

KEY TO TABLE XXXI

Numbers lying along the diagonal line represent the number of patients who had the same score for one parameter (blood pressure or weight) during both treatments. For example, in Part A, 4 of the patients who had two courses of treatment with the combined tablet separated by a variable interval of time had a blood pressure score of 1 during both courses of treatment. For a perfect correlation of scores, all numbers would be on the diagonal line.

TABLE XXXI

COMPARISON OF BLOOD PRESSURE AND WEIGHT SCORES DURING TWO TREATMENTS

(White Patients Only)

A. Two Nonconsecutive Treatments with the Combined Tablet

BLOOD PRESSURE SCORES

2nd Treatment \ 1st Treatment	0	1	2
0	3	1	1
1	1	4	1
2	0	1	2

WEIGHT SCORES

2nd Treatment \ 1st Treatment	0	1	2
0	3	3	3
1	4	1	3
2	0	2	0

B. Two Consecutive Treatments - Combined Tablet Followed by IUD

BLOOD PRESSURE SCORES

IUD \ Combined Tablet	0	1	2
0	4	4	2
1	2	8	1
2	1	1	1

WEIGHT SCORES

IUD \ Combined Tablet	0	1	2
0	6	6	5
1	1	3	1
2	1	1	2

bined tablet to the IUD (part B) the proportion who scored 1 or 2 for blood pressure during the two treatments could not be analyzed, although more appeared to have done so during treatment with the combined tablet lthan during use of an IUD. A significantly higher proportion ($P < 0.05$) had weight scores of 1 or 2 when they used the combined tablet than when they used an IUD, indicating that the weight either remained stable or fell when the combined tablet was discontinued.

Table XXXII shows the combined score applied to patients who had a pregnancy following the use of the combined tablet, Part A for white patients alone and Part B including the five Indian patients in this category. A larger proportion of patients appeared to have high combined scores (4, 5, or 6) during the post-treatment pregnancy than during the treatment but this difference was not significant. Nor was there a significant difference in the proportion of those patients with this high combined score during the post-treatment pregnancy and during pregnancies preceding treatment.

There was no difference in the proportion of white patients with identical combined scores in pregnancies preceding treatment and during treatment and in those with identical combined scores during treatment and in the post-treatment pregnancy.

KEY TO TABLE XXXII

Numbers lying along the diagonal line represent the number of patients who had the same combined score during treatment with the combined tablet as they did during pregnancies following that treatment. For example, in Part A, 1 of the 26 white patients who had a pregnancy following treatment had a combined score of 1 during the treatment and a combined score of 1 during the post-treatment pregnancy. For a perfect correlation of scores, all numbers would be on the diagonal line.

TABLE XXXII

COMBINED SCORES *FOR BLOOD PRESSURE AND WEIGHT CHANGES DURING COMBINED TABLET TREATMENT AND DURING POST-TREATMENT PREGNANCY

A. White Patients Only (26 patients)

Post treat. Preg. Score	Combined Tablet Score 1	2	3	4	5	6
1	1	2	0	1	0	0
2	1	2	0	1	0	0
3	0	0	0	1	0	0
4	2	1	0	2	1	0
5	4	1	1	0	2	0
6	0	0	1	1	1	0

B. Indian and White Patients (31 patients)

Post treat. Preg. Score	Combined Tablet Score 1	2	3	4	5	6
1	1	2	0	1	0	0
2	1	2	0	2	0	0
3	1	0	0	1	0	0
4	2	1	0	2	1	0
5	4	1	2	1	2	0
6	0	1	1	1	1	0

* For explanation of how combined score was calculated see Method.

DISCUSSION

Originally, interest in initiating the present study was stimulated by an article published by Brownrigg (1962) entitled, "Toxemia in Hormone-Induced Pseudopregnancy" which described a case of blood pressure elevation, rapid weight gain and severe headache developing after some months of continuous administration of gradually increasing doses of norethynodrel. Other than the elevated blood pressure, no other stigmata of hypertensive disease were found. The patient's weight and blood pressure returned to the original levels following removal of the uterus. The pathologist reported decidual reaction in the endometrium. In his discussion, the author raised the possibility that the striking arterial hypertension resembling severe toxemia of pregnancy which occurred in this patient might have been related either to the high levels of the hormonal medication or to the extensive decidual reaction following the administration of the hormone.

Following this report, blood pressure recordings were initiated at the Clinic as part of the routine follow-up of patients using the combined norethindrone tablet as a contraceptive. Shortly thereafter, similar changes to those reported by Brownrigg were noted in a patient: these included a sudden weight gain with edema of the face and hands and an elevation of blood pressure to 140/95 mm. Hg accompanied by a severe throbbing headache. Administration of a diuretic relieved the headache, and diuresis with a weight loss of six pounds within 48 hours occurred

with a return of the blood pressure to the previous level. It was considered at that time that patients exhibiting these changes might possibly be those who would later develop, or who had in the past developed, similar changes which would be called preeclamptic toxemia during their pregnancies. Further observations in the Clinic confirmed the fact that a number of young and otherwise apparently healthy women using this cyclic medication had elevated blood pressure recordings at various times during their treatment. Some complained of weight gain, especially in the latter part of the cycle. Some also noted that they had difficulty maintaining their normal weight. Others noted some swelling, particularly of the hands. Some patients complained of "throbbing" or "pounding" headaches either before, during or just shortly after the menstrual period in some cycles. When the blood pressure could be recorded at the time the patient was suffering from these headaches, blood pressure elevation could not be demonstrated. Often, however, the headaches were relieved by the administration of diuretics. On further questioning of the patients, it was noted frequently that they had experienced all of these symptoms during normal unmedicated menstrual cycles.

In her book on the premenstrual syndrome, Dalton (1964) included a whole chapter on the similarity between toxemia of pregnancy and the premenstrual syndrome. Earlier, Greenhill and Freed (1940) had suggested the name "toxemia of menstruation" for the latter syndrome because of the common features of each. Some attempts have been made to correlate the occurrence of these features during pregnancy and the premenstruum in the same patient. Although Dalton calls this a close correlation, Greene and Dalton (1953) noted that toxemia had occurred in only 19 percent of 58 women who suffered from the premenstrual syndrome. Never-

theless, it was considered that something in the hormonal milieu of the premenstrual part of the cycle could produce these same changes described as toxemia of pregnancy and the distinct possibility existed that a patient developing these changes in the one situation might be predisposed to their recurrence in the other.

Based upon this idea, it seemed possible that the sex hormonal status of the patient using a progestagen-estrogen combination could also resemble her condition during pregnancy. Accordingly, it was decided to examine the changes in blood pressure and weight during oral contraceptive therapy and to compare them with changes occurring during pregnancy. Group changes in these parameters during the first contraceptive treatment and the first viable pregnancy were chosen as suitable backgrounds for establishing levels or scores for the degree of variation in the two parameters.

The present study, to our knowledge, is the longest consecutive clinical trial of the cyclic use of norethindrone, 5 mg. in combination with mestranol 0.075 mg. In other studies the patients have been changed to newer lower progestagen-dose compounds. Dickinson and Smith (1963) reported a series of 117 private patients using this preparation and Board (1965) reported a series of 132 medically indigent patients from Richmond, Virginia who used this compound. In this latter study, 117 of the patients were Negro. Rice-Wray, Goldzieher and Aranda-Rosell (1963) had also reported on the use of this medication. Two earlier papers were published which included some of the patients in the present study (Swartz et al., 1963; Chernick, 1965). In both reports, private patients were included and were compared with the Clinic population which was a composite of white and Indian patients. Some differences were noted between the Clinic and

private groups at that time. Therefore, it was decided to limit the present work to the Clinic population in the oral contraceptive study and further to subdivide it by considering the white patients and Indian patients separately. Analysis of initial data and follow-up supported this latter decision.

Board (1965) later made the point that contraceptive methods should be evaluated in various populations because of the differences in effectiveness when used by Clinic patients and private patients. Furthermore, Puddy (1965) in a paper on "The Difficulty of Assessing Subjective Symptoms Relative to Ovulation Inhibition" stressed that social, economic and cultural factors in a population sample affect the subject's motivations and reactions in any clinical trial; as well, the observer adds his own bias to the study. For these reasons she suggested that valid comparisons cannot be made between trials conducted with the same drug by different observers and different population samples even if the methods used were comparable.

Double-blind clinical trials of medications of this nature are difficult if not impossible to perform because the very nature of the effect of the compound, i.e., contraception, raises ethical and practical problems in imposing this type of study design. Among the earliest clinical trials in Puerto Rico using oral contraceptives, a placebo study was done (Pincus, 1965) to evaluate the frequency of "reactions" to the medication in the early cycles. This study was double-blind but all of the subjects were using a conventional contraceptive as well as the tablet. The patients receiving a placebo and an oral contraceptive in one city were told that they were being tested as users of a possible oral contraceptive and they were to note all symptoms. In another city the real oral contraceptive was

given to a group of subjects who were not told to expect any "reactions". The subjects in all three groups were questioned at their monthly visits regarding any complaints. The high incidence of "reactions" in the patients using the true medication in the first study was not significantly different from those patients using the placebo, but it was significantly higher than the incidence in the patients using the medication who had not been admonished to expect certain subjective symptoms.

For these reasons, in the present study, the patients using the IUD were regarded as the next best thing to a control group for comparison of the effects of the oral contraceptive, these patients being drawn from the same population in the Clinic. It is a known fact that the IUD is not one hundred percent effective; therefore, patients could not ethically be assigned at random to either of the two treatments. Patients with numerous subjective complaints using the earlier oral method were offered the choiceof changing to this new contraceptive. The IUD was also favored for patients who were considered incapable of coping with the cyclic method of tablet administration or who would not be likely, or able, to return for regular visits for new supplies. Some patients were referred from private physicians specifically for IUD insertion. Patients with menstrual irregularities were encouraged to choose the oral method. With numerous adverse reports appearing in the press about oral contraceptives, some patients coming to the Clinic for contraception preferred to use the IUD. Other patients had, for example, heard from friends or neighbours that they had gained weight using an oral contraceptive and chose the IUD because they were afraid they would gain weight. (Some of these patients actually did gain weight during the time that they used an

IUD). All patients were advised of the small chance of pregnancy with the device in situ and of the possibility of expulsion of the IUD. After pregnancies began to occur with the device in situ, the advantages of the oral method were stressed when a choice was possible. In addition to this bias in the choice of method, special difficulties were involved in the use of the IUD including irregular bleeding and cramps and occasional expulsion of the device, particularly in the early months of treatment. As experience was gained in the use of the device these complications were better managed.

This non-random assignment to the type of treatment had few significant effects on the composition of the groups in the study.

The proportion of patients with elevated blood pressures at the start of the first contraceptive treatment seemed high. In the Health Examination Survey (HES) performed in the United States from 1960 to 1962, the blood pressure was determined in a very large sample of the population and age-specific distributions of systolic and diastolic blood pressures are presented in graphic form for each sex (Gordon, 1964a). In the present series, a slightly lower percentage of the white patients under 35, and 35 and over had a systolic pressure of 140 mm.Hg and over than in the HES. The number of Indian patients in the under 35-year old group with a systolic blood pressure of 140 or over approximated the percentage in the HES; in the 35 and over age group there were too few Indian patients to make a valid comparison.

The proportion of under 35-year old white and Indian patients in our study with a diastolic pressure of 90 mm.Hg or higher was higher than in the HES. In the over 35-year old whites, however, the percentage with this diastolic level

approximated that given in the HES for patients 35 to 44 years of age. Only a few patients were 35 or over in the Indian group. In an analysis of the data according to race (Gordon, 1964b), the HES only considered Negro and white patients but presented no statistics on the North American Indian.

The division of weight percentile and height percentile categories into the ratios used in this study masked the effect of some very obese tall women whose weight and height percentiles would be classified in the same grouping. There was a large percentage of patients, however, with a very high weight percentile category (greater than the 75th) whose height percentile was below this level, and usually considerably below. This was particularly true in the Indian patients.

When the author presented preliminary reports of part of this series (Chernick, 1964a and 1964b), it was evident from the discussion that regular blood pressure recordings were not at that time part of the usual follow-up of patients using oral contraceptives even in clinical trial situations. Indeed, the FDA report on the Oral Contraceptives (Food and Drug Administration Advisory Committee on Obstetrics and Gynecology, 1966) contains no mention of possible changes in arterial pressure.

In a discussion of papers presented at a Symposium in Sydney (1965) there was no consensus as to whether increases in blood pressure did occur in association with oral contraceptive therapy. Some of the participants mentioned some outstanding cases they recalled with excessive weight gain whose blood pressure was elevated and MacIntosh went so far as to say that this occurred particularly in anybody with a bad history of toxemia of pregnancy. The results of the present study tend to show that, in general, clinical impressions tend to bring forward in

one's memory those outstanding cases which have come ton one's attention but which may not represent the general rule or, in fact, any deviation from the behavior of the normal population.

Owen (1966) reported a case of blood pressure elevation during contraceptive therapy with a norethynodrel combined tablet. The pressure fell when the medication was withdrawn and a diuretic administered. He wondered whether this hypertension was due to "pseudotoxemia" or to "coincidence". In reply to this letter, Hutchings (1966), Medical Director of Searle and Co., stated that "extremely few reports have been received of hypertension associated with the use of oral contraceptives. Indeed, the reported incidence parallels that expected in the untreated female population at risk." In the present study, no patients were taken off the medication because of an elevated blood pressure reading; indeed, the results show that in some cases, the blood pressure went down even though the medication was continued (Figs. 1a and b).

In assessing blood pressure changes, the levels which were called elevated were chosen in accordance with the definition of toxemia of pregnancy outlined by the American Committee on Maternal Welfare (Eastman and Hellman, 1965). Although some difference existed at the beginning of the first treatment in the age distribution of white patients using the two contraceptive methods, there was no overall difference in age distribution of either the systolic or diastolic blood pressures at the initial readings. Similarly there was no obvious relation between age and initial blood pressure distribution in the Indian patients, although generally more of them had elevated initial systolic blood pressures than did the white patients. Various comparisons showed that the only statistically significant

difference in the distribution of patients fulfilling the criteria for an elevated blood pressure occurred between the white patients using the combined tablet and those using an IUD when only those patients who met the criteria on more than one occasion were considered. This difference, though only at the five percent level of significance, may be due to a number of factors.

In general, the percentage of patients meeting the criteria rose with each succeeding cycle group except for those using an IUD for more than ten cycles. It should be noted, however, that 17 times as many white patients and eight times as many Indian patients were followed on the combined tablet for more than 10 cycles as on the IUD; furthermore, those using the combined tablet in this category had completed up to 60 cycles whereas those using an IUD had never gone past 20 cycles. More blood pressure readings were obtained in those using the combined tablet than in those using an IUD because the former had to return periodically for further supplies. In addition, 42 of the 49 white patients using the combined tablet who had more than one elevated pressure reading over their whole course of treatment had completed more than 10 cycles whereas neither of the two patients using an IUD had. Further support is given to the idea that the more times the blood pressure is measured the more likely an elevated level will be found by the observation that the percentage of patients in all groups who fulfilled the criteria for blood pressure elevation on the basis of the interval between the lowest and highest readings increased with the length of treatment.

Additional support is lent by the known variations in blood pressure readings: for example, in the HES (Gordon, 1964a), a variation of 10 mm. Hg or more systolic

pressure and at least 6 mm. Hg diastolic pressure for one-half the subjects examined, occurred between three readings within one single physical examination. Glock, Vought, Clark and Schweitzer (1956) studied the variability of daily blood pressure measurements in the same individuals over a three-week period and determined resting levels six times every weekday during this period. The median range for the three weeks was 30 mm. Hg systolic and 22 mm. Hg diastolic. The author found (Chernick, 1963) wide variations in daily readings of blood pressure in a group of 31 student nurses (19-21 years old) who were recording several physiological parameters during the menstrual cycle. A surprising amount of diurnal variation also occurs in blood pressure (Richardson, Honour, Fenton, Stott, and Pickering, 1964). This latter effect was minimized in the present study because all clinic measurements were made in the afternoon.

Because the period of observation varied widely from patient to patient and was usually longer for those using the combined tablet than for those using an IUD, it was decided that the comparisons of blood pressure changes would be more valid if a fixed period of observation (involving a similar number of blood pressure readings) were employed. Such an analysis showed that when only the first ten cycles of treatment were considered for those patients who had completed at least ten cycles, there was no statistically significant difference between the proportions of patients in each treatment group who met the chosen criteria for elevated blood pressure.

An analysis of the variation in elevated recordings in relation to the initial blood pressure showed (Figs. 1a and b) that the same proportion in all

treatment groups had elevated readings in all three cycle groupings regardless of the initial pressure. In at least one-half of the white patients, regardless of initial blood pressure, the elevation was variable from one cycle grouping to another. It is of interest that a significant proportion of patients who had elevated blood pressure readings at their initial visits, never had elevated pressures again even though some were followed for more than 10 cycles.

Although there has been considerable discussion concerning arm girth and indirect blood pressure measurements, studies suggesting "that for a given direct blood pressure the indirect blood pressure tends to rise as arm girth increases, are still too scanty to provide accurate estimates of the numerical extent of this effect, or indeed to prove that such an effect exists." (Gordon, 1964a). From the Figures in the HES, it appears that for arm girths between 24 and 38 cm., the rate of increase in blood pressure with age is practically uniform. Moreover, the blood pressures differ by less than 10 mm. Hg between the smallest and largest arm girths for women of any one age.

Almost all papers on clinical trials or side effects of oral contraceptives have mentioned weight change and, particularly, weight gain. The proportion of these changes varies from study to study and from compound to compound within these studies. Wiseman (1965) encountered no weight trends with norethindrone (2 mg.) combined tablets, about the same percentages of patients gaining as losing

three pounds or more. In Board's (1965) study, the commonest weight change was a gain of six to 10 pounds; only nine of 132 patients lost weight. Thirty percent of the patients in Dickinson and Smith's study (1963) reported a weight gain of more than three pounds while two percent lost weight. In a study using continuous high-dose treatment (Liggins, 1965), norethindrone was shown to be associated consistently with weight gain, even with estrogen added to its acetate whereas medroxyprogesterone acetate was associated consistently with a weight loss. Similarly, Drill (1965) concluded that the incidence and amount of weight gain is greater with norethindrone compounds than with those containing norethynodrel.

There has been some discussion as to the cause of the weight gain during oral contraceptive therapy. Mears (1965) reported that many patients using the 19-nor testosterone derivatives experienced an increase in appetite in the early part of their therapy "similar to that of early pregnancy", but that this waned after three or four cycles. The increased appetite was usually associated with weight gain. On all different kinds of oral contraceptives the weight gain was marked in some patients but, even in them, the weight plateaued after the first year. She suggested that weight gain may be of two types associated with different kinds of medication—fluid retention which may be associated with premenstrual tension from estrogenic medication, and an anabolic effect from progestagenic medication. In discussing the properties of oral contraceptives, Drill (1965) noted that norethindrone has minimal androgenic activity on bioassay.

As early as 1943, Taylor and Sprunt demonstrated increased extracellular fluid in the skin of rabbits following intraperitoneal injection of estrogen. Other

studies showed that sodium, chloride and water retention followed estrogen injection in dogs and significant hemodilution occurred on short-term estrogen administration to oophorectomized women (Witten and Bradbury, 1951). Preedy and Aitken (1956) undertook a study of the effect of estrogen on water and electrolyte metabolism based on three observations: "estrogens are related chemically to the strongly sodium-retaining steroid desoxycorticosterone; the recurrent ankle edema observed in some women before menstruation was considered by Fluhmann to be associated with an increase in blood estrogen levels; and the edema frequently found in late pregnancy occurs at a time when estrogen production is at its height." They found no sustained effect of estrogen injections on weight, urinary water, sodium or chloride. A temporary storage with a concommitant increase in extracellular fluid volume was followed by diuresis. They postulated that the weight gain they observed may be partly due to anabolism. Klopper (1959) noted that in pregnancy and during the menstrual cycle, changes in plasma water follow changes in estriol excretion very closely. When he administered estrogen to postmenopausal women, the volume of total body water and of plasma water increased due to massive retention of fluid.

In her study, Liggins (1965) showed that the main contribution to the weight gain with a combined tablet was made by the progestagen, particularly 19-nor testosterone derivatives. She did not attempt to distinguish between water retention and anabolism as the possible causes of the weight gain and suggested that other factors might have been operating, such as a sense of well-being, associated with the 19-nor testosterone derivatives, which may stimulate appetite. In the discussion of her paper, Liggins remarked that following cessation of therapy

a slowly progressive loss occurred. If the weight gain were mainly due to water retention, then a rapid loss might have been expected. Furthermore, diuretic therapy did not alter the long term weight change associated with oral hormone preparations. Balance studies in progress at that time had not shown any clear-cut evidence that the compounds were truly anabolic. In the same Symposium, Grounds (1965) reported a series using another compound in which two cases gained from 15 to 20 pounds in a year. According to him, these patients denied a greatly increased caloric intake and he suggested that they were "extremely sensitive to the anabolic effect which most progestational agents have to some degree". It may have been, however, as is the case in many people who have a tendency to gain considerable amounts of weight, that what they claimed as their oral intake bore no actual resemblance to what they did eat. McBride (1965) felt that the weight gain in the majority of patients on oral contraceptives was due to fluid retention and that only a small group had an anabolic effect from the 19-nor testosterone derivatives. He commented on the complaints of patients using oral contraceptives of swelling of their hands and feet and tightness of their clothing. These latter symptoms are a common part of the premenstrual syndrome frequently observed in patients not using these medications. Pincus (1965) pointed out that patients using oral contraceptives may gain weight because of a relief from anxiety about accidental pregnancy with consequent improvement in their appetites.

In a recent paper, Bakker and Dightman (1966) in studying the combined tablet containing norethynodrel classified side effects into three groups: "Type 1. Pharmacologically induced side effects, which are specifically the result of chemical changes induced in the patient's organism Type 2. 'Scapegoat' side effects,

which are primarily the result of increased self-observation and the need to make what is new and unfamiliar understandable Type 3. Suggestion-induced side effects, which are the result of a complex set of expectations that the patient has acquired concerning drugs". Weight gain was one of the side effects they examined because in other studies on the compounds, patients had complained of weight gain due either to fluid retention or to accumulation of fat. In their study, there were no significant trends in weight change, although fluctuations occurred with time between individuals and within the same individual; over the course of the study the fluctuations balanced each other out. The authors concluded that they had no evidence to support the hypothesis that the compound caused an actual weight gain due to increased fat deposition. Some patients, however, complained of weight gain and others of weight loss which they attributed to this medication. The authors classified this as a "scapegoat" side effect because the patients refused to accept personal responsibility for their own weight change. In patients who discontinued the medication for one month, there was a definite loss of weight, which was regained when the medication was resumed. This was assumed to indicate a weight loss due to diuresis and subsequent fluid retention when the medication was restarted. Bakker and Dightman concluded that in the use of the norethynodrel compound, fluid retention occurred in approximately 30 percent of women. This was an all or none effect, quite obvious in those affected. They therefore classified fluid retention as a "pharmacological" side effect of the medication.

In the present study, there was considerable variation in weight change during contraceptive treatment as shown by the large standard deviations even in

those groups where the mean weight changes were significantly different from the initial weight. In other words, although some patients gained considerable weight, others actually lost weight during the treatment. The mean maximum weight changes of both the white and Indian patients using the combined tablet increased as the length of the treatment increased, the changes in all cycle groupings being higher in the Indian patients than in the white. The reverse was true in the white patients using an IUD; whereas weight gains of approximately the same magnitude did occur in the Indian patients using an IUD as in those using the combined tablet. These finds may reflect two factors: (1) that there is indeed a tendency for weight gain to be associated with oral contraception with this particular medication in some patients; (2) white women may tend to be more weight conscious than Indian. From the initial data at the beginning of the study a higher percentage of Indian patients had weight percentile to height percentile ratios for their age greater than 1 and usually very much greater than 1. Some women chose the IUD because they were afraid of weight gain and consciously controlled their weight while using this latter contraceptive. Indian patients using an IUD did not gain weight as significantly as did those using the combined tablet, although the mean weight changes were of the same order, possibly reflecting this cultural trend.

Another explanation of weight gain in some patients using oral contraceptives may be the "scapegoat" side effect referred to by Bakker and Dightman (1966). Certainly some patients who do gain weight and even some who complain of weight loss are quick to blame this on the medication they are using and are loathe to examine in detail their dietary habits.

Eastman and Hellman (1965) claimed an incidence of toxemia in late preg-

nancy of six to seven percent. Tatum (1966) quoted an average incidence of four percent, varying from one to 10 percent of all pregnancies, influenced by a number of factors, but generally varying inversely with the quality of prenatal care provided. Zuspan (1966) indicated that prenatal care with early recognition of toxemia and its aggressive management has reduced the incidence of eclampsia. In the present series, more than 50 percent of the white patients and a higher percentage of the Indians, who had data available on their first viable pregnancy, actually fulfilled the hypertensive criteria of the American Committee on Maternal Welfare (Eastman and Hellman, 1965) for toxemia of pregnancy.

A possible explanation for the discrepancy between the incidence of toxemia quoted by textbooks of Obstetrics and that recorded in this study is that all blood pressures recorded were considered in making the diagnosis. Only 17 percent of the hospital and clinic charts of the white patients and 28 percent of those of the Indian patients, however, noted any abnormalities related to toxemia during this pregnancy. If official incidences are quoted from diagnoses on hospital charts, obviously many cases which meet the blood pressure criteria will be missed. Only prospective studies with close follow-up will demonstrate whether these criteria are really related to the prognosis for the mother and fetus, or whether they will eventually be shown merely to select those patients who may later develop hypertension.

Many of the first viable pregnancies in the present series occurred up to 20 years ago when there were different standards of prenatal care in Clinic patients than exist today. It should also be noted that these were indigent patients who frequently did not attend a physician until late in their pregnancy and who were

negligent in returning for regular visits. The Indian patients attended Prenatal Clinic even less frequently than did the white patients.

It is of interest that it was the diastolic pressure particularly that was elevated in these patients. The choice of these absolute levels by the Committee, that is 140 mm. Hg. systolic and 90 mm. Hg diastolic pressure, received some support in the paper by McClure Browne (1961) who surveyed clinical aspects of eclampsia in Britain. The mean blood pressure of a large series of women at 20 weeks of gestation was found to be 124/73 mm.Hg in the 15- to 30- year olds and the level two standard deviations above this mean was 140/90. In patients over 35 years of age the mean was 127/77 mm.Hg and the level two standard deviations above that was 154/90.

MacGillivray (1961) found that the actual blood pressure level reached was more important than the rise in pressure as a prognostic factor in perinatal mortality in primigravid patients. He classified blood pressure changes after the 20th week of gestation into three general groups. The first was a "low" group with a diastolic blood pressure less than 90 mm.Hg at 20, 30, 36 weeks and at the last prenatal visit before delivery (62 percent). The second group was called "labile" with a diastolic pressure intermittently above 90 mm.Hg with no steady increase from 20 to 40 weeks (20 percent). The third or "rising" group had a steady increase so that the last predelivery reading was always greater than 90 mm.Hg (18 percent). He found a similar percentage classification if a systolic blood pressure of 140 mm.Hg was used instead of the diastolic outlined above.

McClure Browne (1961) found that a rise in blood pressure had no effect on the prognosis for perinatal mortality or abruptio placentae unless it was greater

than 60 mm.Hg systolic or 50 mm. diastolic pressure.

Chesley (1964) in analyzing 19 publications with a total of 11,960 cases arrived at an average figure for total weight gain in a normal pregnancy of 24.0 pounds with a standard deviation of 10.8. This closely resembles the mean maximum weight gain in both the Indian and white patients in our series in the first viable pregnancy. There is some question as to whether the maximum weight gain has any relation to the development of toxemia. Dieckmann and Brown (1938) found that 57 percent of about 570 preeclamptic patients gained less than 22 pounds and 71 percent gained less than 26.5 pounds. In a review of maternal deaths from toxemia in Ontario from 1958 to 1961, Kinch (1963) stated that excessive weight gain is not an invariable precursor of the development of toxemia of pregnancy but it is often the earliest sign. He stressed particularly the value of a sudden gain in weight as an early premonitory warning although the officially accepted definition of toxemia of pregnancy makes no mention of weight gain. Theobald (1962) advocated weekly antenatal visits from the 24th week onwards in order that this warning might be heeded and vigorous treatment in the prehypertensive phase of toxemia might prevent later tragedy. Earlier MacGillivray (1961), whose study had been concluded in 1956 before weight gain restriction was practised in Aberdeen, found that a weight gain over 1.25 pounds per week between the 20th and 30th weeks gestation was followed by a high incidence of albuminuria and edema with unfavorable prognostic significance in the consideration of prematurity and consequent perinatal mortality from toxemia. Tatum (1966) noted that a sudden gain in weight is the first and most consistent indication of developing preeclampsia and quoted a weight gain exceeding one pound per week at

any time from the 20th to the 34th week of pregnancy as indicating an abormal degree of water retention. After that time, a weekly weight gain of 2.5 pounds or more should warn of impending toxemia. He stated unequivocally that this rapid weight gain is due to water retention which may be followed by clinically apparent edema, although 11 pounds of water may be accumulated without edema being evident.

Stevenson (1952) observed that all patients who gained more than four pounds in a month deserved closer prenatal follow-up and if they gained this much in two one-month intervals, preeclampsia was usually inevitable. He also felt that overweight pregnant patients at the beginning of pregnancy were most prone to develop preeclampsia. Eighty percent of 144 patients who weighed more than 133 pounds at the onset of pregnancy developed preeclampsia whereas only 48 percent of 356 patients less than this initial weight did develop preeclampsia.

In relating body type to performance in pregnancy, Chesley, Somers and Vann (1948) noted that the higher the weight-height ratio at the postpartum check-up, the more likely toxemia would be to recur in a later pregnancy. Lowe (1961), in a large survey of patients in Birmingham, found that toxemia was related to the "body build".

Fields and Davis (1962), divided patients into those weighing 150 pounds or less and those over 150 at the onset of pregnancy taking into account their height. When various problems of pregnancy and delivery including prolonged labor, incidence of Caesarean section, prematurity of the infant, postpartum hemorrhage, toxemia and hypertension, in particular, were considered, the percentage incidence increased as the weight category of the patient rose. In over

one thousand patients, Emerson (1962) classified 55 percent as normal or underweight, 25 percent as intermediate, and 20 percent as overweight. He found that those in the overweight category had seven times as many blood pressure recordings equal to or greater than 140/90 mm.Hg as the "normal" group. Besides other complications associated with this overweight group, he found that the rate of preeclampsia was five times the "normal". When Myles (1964), related preeclampsia to body type, he found that this condition occurred most frequently in fat or endomorphic women and was less common in muscular types. In The Physiology of Human Pregnancy, Hytten and Leitch (1964) found that the incidence of preeclampsia rose as the mean weight gain per week increased, a steep rise occurring after 1.25 pounds per week. They quoted Thomson and Billewicz (1957) who found that patients who were overweight at the 20th week had an increased incidence of preeclampsia.

Hamlin (1958) noted a typical appearance, i.e., edema and obesity, at 16 weeks gestation of those patients who, in the last ten weeks of pregnancy, became severely preeclamptic with elevated blood pressures. Stevenson (1952) also claimed that the preeclamptic could be detected in early pregnancy and Dieckmann (Hamlin, 1958) was able to recognize the facies of an impending preeclamptic at 13 weeks' gestation. Hamlin (1952) had stressed dietary measures in prophylaxis against toxemia and noted that a weight gain of eight pounds or more in any 10-week period before 30 weeks' gestation was an indication of the onset of "prehypertensive" preeclampsia.

In the present study, a significantly higher percentage of Indian than white patients began the first viable pregnancy with a ratio of weight percentile to

height percentile greater than 1. Also, a higher percentage of Indian than white patients fulfilled the hypertensive criteria for toxemia of pregnancy. In the white patients, there was some relation between interval weight gain (which probably reflected water retention) and maximum weight gain. Furthermore, approximately 50 percent of patients in both groups gained three pounds or more in any one-week interval during the first viable pregnancy. Since prenatal visits at one-week intervals were usually in the last few weeks of pregnancy, therefore, this interval weight gain could be regarded as an indication of impending toxemia of pregnancy in these patients.

Although, as noted above, there is a discrepancy between the incidence of toxemia as defined in this study and that quoted in textbooks, it is interesting that the results show that approximately the same percentage of patients gained three pounds or more in any one week as fulfilled the official hypertensive criteria for toxemia of pregnancy. It would appear imperative, therefore, that any prospective study of the problem of toxemia of pregnancy should include frequent recordings of weight as well as blood pressure.

McCartney (1966) pointed out the current dissatisfaction with the standard definition of toxemia of pregnancy and its classification. Similar dissension exists over the terminology applied to blood pressure, particularly in the classification of hypertensive and normal pressures (McIver, 1964). This seems reasonable in view of the fact that the etiology and true nature of both of these conditions is unknown. Consequently, in this study, data from the population observed were employed to devise scoring for both blood pressure and weight for comparisons during contraceptive treatment and pregnancy. Including single recordings of

blood pressure elevation in the scoring system seems justifiable despite the specification of the American Committee on Maternal Welfare (Eastman and Hellman, 1965) because any elevation is an indication of the potential behavior of the patient's vascular system and should be regarded as a "forewarning of future hypertension" (Bryans, 1966).

A large proportion of every group had patients whose scores were not identical during treatment. During both treatments in the white patients, an equal proportion had elevated scores (1 or 2) for weight and for blood pressure. In the Indian patients using the combined tablet, a higher proportion tended to have elevated scores for blood pressure than did for weight. In the Indian patients using an IUD, on the other hand, the reverse trend was indicated with significantly more scoring high for weight than for blood pressure. This is difficult to interpret.

When the correlation of the scores during pregnancy alone was considered a higher proportion had elevated scores (1 or 2) for blood pressure than for weight in all groups. This latter result may indicate that either weight changes were not being detected or their record was not available for this study or that weight gain is, in fact, a less reliable early sign of preeclampsia than was considered above. The most likely explanation is that these patients had few prenatal visits at the hospital Clinic and, therefore, little record of weight gain, whereas almost all had blood pressure readings during their hospital admission for delivery.

When white patients who used the combined tablet for more than one nonconsecutive treatment were considered, an equal proportion of patients had ele-

vated scores during both treatments for both blood pressure and weight. Among patients who changed from the combined tablet to the IUD, similar proportions had elevated scores for blood pressure while they used the combined tablet and when they later used an IUD. A significantly higher proportion, however, had elevated scores for weight when they used the combined tablet than when they used an IUD. This latter finding may reflect the motivation of the patient to control her weight at the time that she changed contraceptive measures.

A significantly higher proportion of patients had elevated scores for both blood pressure and weight during pregnancy than during either type of contraceptive treatment. This effect, though still significant, was not as great when the weight scores were compared in the white patients during pregnancy and during treatment with the combined tablet as it was in those patients who used an IUD; nor was it as great when the weight scores were compared in the Indian patients who used either treatment. This reflects the earlier finding of significantly elevated mean weight changes during the first treatment in these three groups.

A greater proportion of patients had high combined scores during pregnancy than during any of the treatments. It may be that pregnancy is a stronger stimulus to the kind of blood pressure and weight changes chosen for consideration than either exogenous or endogenous hormones in the non-pregnant woman of reproductive age.

In the small group of patients who had carried a pregnancy to term following cessation of the combined tablet, there was no significant difference between the proportion who had high combined scores during treatment and in the later pregnancy. A larger sample would be necessary before definite statements could

be made as to why a relatively lower scoring was found in this posttreatment pregnancy than in all the pregnancies preceding the contraceptive treatment. Prospective studies of pregnancies are necessary to obtain complete data for evaluation.

Hypertension, Toxemia and Oral Contraceptives

In the last 50 years there has been considerable discussion as to whether toxemia of pregnancy predisposes patients to the development of later essential hypertension arising from the finding that hypertension often persists in patients who have suffered from toxemia. Theobald (1936) observed that blood pressures of women suffering from hypertension tend to fall during the first half of pregnancy and this was later supported by F.J. Browne (1947). Thus, many women whose blood pressure was recorded as normal at the first visit to a prenatal clinic actually suffered from hypertension before they became pregnant. In a long-term follow-up of all patients at the Margaret Hague Hospital who experienced eclampsia in their first pregnancy since 1931 Chesley, Somers and Vann (1948), discussing whether toxemia caused hypertension or was merely an acute and specialized manifestation of latent hypertensive disease, stated that a continuing toxemia led to vascular damage which caused persistent hypertension. They did, however, relate that other studies showed no difference in the incidence of hypertension in nulliparous and parous patients. On the other hand, in the fourth periodic report (1962) of this study Chesley, Cosgrove, and Annitto stated that eclampsia does not cause hypertension, but precipitates its early appearance. Just as a declared essential hypertension predisposes the patient to the development of preeclampsia,

so may latent hypertension or the hypertensive diathesis predispose to the development of preeclampsia. They concluded that women who have eclampsia in the first pregnancy are no more likely to develop hypertension ultimately than unselected women. These views were strongly supported by Bryans (1966). In discussing the prognostic significance of recurring toxemia of pregnancy, Chesley, Annitto, and Cosgrove (1964) quoted Dieckmann's earlier opinion that recurring toxemia is an expression of latent hypertension which would have developed in later life had there been no pregnancies. In contrast to Chesley's studies, Barnes and Browne (1945) found that the incidence of hypertension was higher in all age groups in nulliparous than parous women. Kellar (1950) concluded that preeclampsia probably did not cause essential hypertension. Browne (1949) changed his position somewhat, indicating that pregnancy may cause the hypertension in a susceptible patient to be manifest earlier than if she had not become pregnant.

Following publication of the early report of this present series, Hertzman (1965) in a letter on the development of moderately severe hypertension in two patients using the norethynodrel compound wrote that one had a hypertensive toxemia preceding her treatment. He was concerned with the relation between salt and water retaining properties of the drug and the early (sic) development of hypertension in his patient.

In discussing the remote prognosis of preeclamptic toxemia, F.J. Browne (1958) stated that whether or not the patient developed chronic hypertension immediately following a preeclamptic pregnancy seemed to depend on the presence or absence of a family history of chronic hypertension. Patients with a

family history of this latter condition are more likely to develop hypertension. In these cases, the preeclampsia did not actually cause the hypertension but merely hastened its development. Browne stated that there was evidence that the longer the hypertension of toxemia had lasted before delivery the more likely the chronic disease was to develop. This latter point has been given as an explanation of the apparent paradox of a reportedly higher incidence of residual hypertension following preeclampsia than following eclampsia (Bryans, 1966). According to Bryans, however, this paradox was based on the false premise that eclampsia does, in fact, occur like "a bolt from the blue" whereas in reality it is "the end result of long-standing, neglected, and gradually progressing preeclampsia" the actual duration of which is not known.

There is still some discussion as to whether a family history of hypertension favors the development of toxemia. Theobald (1955) postulated that the hypertension of pregnancy is often hereditary. Schwarz (1963) found that if the family history indicated a hereditary hypertensive disposition, essential hypertension was most likely to start during a pregnancy. Chesley, Cosgrove, and Annitto (1961) found that the incidence of toxemia in the sisters and daughters of eclamptics was five times the general incidence of this condition at the Margaret Hague Hospital. Doyle and Fraser (1961) showed an increased vascular reactivity in the sons of hypertensive men at a time when the sons had not yet developed hypertension themselves, indicating the possibility that much of the heightened vascular reactivity in established hypertension is genetically determined. Chesley (1966), in testing vascular reactivity in normal and toxemic pregnancies, found some differences in reactions to norepinephrine and angiotensin but stated that the

differential reactions were not sufficiently consistent to be of much value in separating preeclamptic patients from hypertensive patients. In a study by Hamilton, Pickering, Roberts and Sowry (1954) and in a later one by Miall and Oldham (1963) there were definite indications that arterial blood pressure, although increasing with age in the general population, may be genetically determined, and that at any one age the relatives of hypertensive patients have higher blood pressures than relatives of nonhypertensive patients. There is some discussion as to whether this is determined by a single gene or numerous genes.

MacGillivray's findings (1961) supported the hypothesis that in some women a hypertensive tendency which becomes manifest in pregnancy produces preeclampsia, and those patients go on to have permanent hypertension in later life.

It is interesting that there is a difference in blood pressure levels in males and females at all ages (Gordon, 1964a). Under the age of 45, blood pressures are higher for men while over the age of 54, women have higher levels. These latter findings relating the incidence of elevated blood pressures to sex may be related to hormonal status where the vascular bed of a female is affected during her reproductive life so that even after the menopause she is able to tolerate higher levels of blood pressure than males.

In a review article on "Recent Advances in Hypertension", Wilson (1964) indicated that changes in volume control may lead to sodium retention with expansion of the extracellular fluid volume and plasma volume raising blood pressure by increasing cardiac output. Dahl and Schackow (1964) reviewed their findings on the effect of chronic excess salt ingestion in the rat. Their genetic studies

showed that chronic salt feeding induced high blood pressure in some but not all rats in an unselected series, but selective breeding produced "sensitive" and "resistant" strains by the third generation. In each strain at every level, the response of males was higher than females. Dahl and Schackow (1964) concluded that the genetic background critically controls the response to factors used to induce experimental hypertension, indicating possibly a genetic-environmental interaction. They also suggested the possibility that similar interactions operate in the hypertensive process in man. In humans, it may be postulated that a sensitivity to a hypertensive stimulus, such as chronic salt ingestion or sodium retention, may precipitate the manifestation of a latent hypertension. This tendency may be inherited as a graded effect and the development of hypertension during pregnancy in a larger proportion of patients than ever become hypertensive in later life may indicate that these patients never receive as strong a stimulus again. Also, after the first pregnancy, their vascular system may be able to tolerate this stimulus better than it could in the first encounter, explaining the higher incidence of preeclampsia in the first viable pregnancy.

It was originally felt that sodium and fluid retention in patients using oral contraceptives may lead to a similar revelation of the hypertensive tendency. Similar findings in patients on an unmedicated menstrual cycle, however, tend to show that this is not a particularly strong stimulus relative to normal hormonal production during the menstrual cycles. Hormonal therapy may be a sufficient stimulus to reveal a latent hypertension and cause its chronic development in some patients, although again this does not seem to be evident from the study of time trends and the proportion of patients on both types of contraceptive therapy who

had elevated recordings in all three time cycles considered in the present study.

Another factor not previously considered and not evaluated in the present study, because of inaccurate diagnoses in retrospective studies of this kind, is the effect of chronic renal disease on the incidence of elevated blood pressure both during pregnancy and during contraceptive therapy. Theobald (1955) said that pregnancy hypertension may be associated with an unsuspected renal lesion occurring probably more often than is realized. McCartney (1966) conducting a study of renal histology assessed by biopsy found evidence of chronic renal disease in 25 percent of primigravidas fulfilling the clinical criteria for preeclampsia and 21 percent among multigravidas fulfilling the clinical criteria for chronic hypertensive renal vascular disease with superimposed toxemia. Because of this, "chronic renal disease plays a more important role in the hypertensive disorders of pregnancy than current statistics indicate". Shapiro (1963) reported on studies in rats showing that chronic pyelonephritis is usually not the cause of hypertension, but it can aggravate a preexisting hypertension and render a nonhypertensive rat more vulnerable to other hypertensive stimuli. An increased susceptibility to contract pyelonephritis was demonstrated in the rat with acute as well as chronic elevation of blood pressure. Shapiro concluded, by extrapolating from evidence in the rat, that it is possible that chronic pyelonephritis increases the susceptibility to hypertensive disease, that pyelonephritis aggravates a preexisting hypertension and that patients with hypertension are more susceptible to the development of pyelonephritis.

Proposals for Further Investigation

Further long-term studies of patients using the oral contraceptive and a

comparable control group are necessary to clarify this situation; studies using selectively bred rats to test this medication as a possible hypertensive stimulus would also be of great interest. Observations related to the menstrual cycle would be valuable in identifying the effect of water retention in weight gain. It is possible that the changes occurring in some patients using the IUD (unmedicated control group) may be related specifically to hormonal changes during the premenstrual part of the cycle whose similarity to toxemia of pregnancy has been noted by Dalton (1964). A study could be designed to match pairs of patients for age, parity, weight-height status, and initial blood pressure for observations at similar points in their menstrual or medicated cycles. A simple adjunct in following weight changes and establishing weight status would be to use the skinfold measurement over the triceps which is readily accessible. Persuading subjects to participate in more complex studies of body composition is rather difficult but studies of total body water and more elaborate studies of blood volume would also be indicated. Furthermore, recalling these patients at five-year intervals for reexamination and blood pressure recording would be a valid approach to the ultimate assessment of possible long-term effects of these contraceptives and the elucidation of the role of the oral contraceptive compound in hypertension.

SUMMARY AND CONCLUSIONS

1. Observations of a toxemia-like syndrome in some patients using progestagen-estrogen medication led to a study of 715 women attending the Clinic at Victoria Hospital, London, between August 1961 and June 1966. Of these, 592 were white, 118 were Indian and 5 were Negro. Oral contraceptives were given as first treatment to 477 white, 95 Indian and 4 Negro women. Insertion of intrauterine devices (IUD) began at the Clinic in August 1964: 115 white, 23 Indian and 1 Negro.

2. The cyclic use of norethindrone 5 mg. in combination with mestranol 0.075 mg. (Ortho-Novum 5 mg.) - called here "combined tablet" - was prescribed for all new patients desiring oral contraception, except between March to August 1965, when cyclic use of mestranol 0.08 mg. in sequence with norethindrone 2 mg. ("sequential tablet") was prescribed for a total of 44 white and 4 Indian patients.

3. Some patients were followed for more than one course of treatment using one or more of the above contraceptives.

4. Reasons for discontinuing or changing treatment or not returning to the Clinic were classified into four groups:

   a) reasons unrelated to method, e.g. moving away, hysterectomy, etc.,

   b) failure or unacceptability of method, c) subjective complaints, possibly

related to method --- smallest group, d) reason unknown --- largest group.

5. Not all patients were included in analyses of the series: because they had a chronic illness (diabetics), because there were too few in the group (Negroes), or because of inadequate initial data.

6. To study the effects of oral contraceptives, patients using an IUD, drawn from the same population, were regarded as "unmedicated controls". Because double-blind studies and random assignment to treatment were not possible in the Clinic, the characteristics of the groups at the beginning of the first treatment were examined. Indian and white patients were analyzed separately.

7. Few important differences existed between treatment groups within each race, but there were some differences between races.

8. Analyses of those patients followed while they used the combined tablet or an IUD as the first treatment showed that a higher percentage of patients using an IUD in the 28- to 35-year old age group contributed the most to a significant difference in the age distribution among the white patients. More of the total Indian patients than the total white patients tended to have had more than four viable pregnancies.

9. Significantly more Indian patients than white patients had elevated systolic blood pressures, particularly in the older age groups. The diastolic blood pressure was elevated in significantly more white patients than was the systolic pressure.

10. More Indian than white patients had a ratio of $\frac{\text{weight percentile}}{\text{height percentile}}$ greater than 1, and fewer had a ratio less than 1.

11. Changes in blood pressure and weight during the first treatment were examined

over three periods: 1-5 cycles, 6-10 cycles, all cycles over 10. The only difference in patients fulfilling the criteria chosen for elevated blood pressure was that more white patients using the combined tablet than white patients using an IUD met the criteria more than once during their whole treatment, ($P<0.05$). Patients who used the combined tablet were followed much longer, had more blood pressure readings, and most of those who met the criteria more than once used the tablet for more than 10 cycles.

12. When the comparison was standardized so that only the first 10 cycles of treatment were considered for those patients who had completed at least 10 cycles, there was no statistically significant difference between the proportions of patients in each treatment group who met the chosen criteria for elevated blood pressure. Although no important elevations of blood pressure were observed during contraceptive treatment with the combined tablet in this study, a more rigidly controlled investigation would be necessary to rule out the possibility of such an effect.
13. Regardless of their initial blood pressure, the proportion of patients in both treatment groups who met the criteria for elevated pressure in all 3 cycle periods was the same except that more Indian than white patients who used the combined tablet did this. A significant proportion of patients with initially elevated blood pressures never had elevated pressures recorded throughout the course of their treatment. Therefore, in this study, there was no consistent pattern of blood pressure change during contraceptive treatment.
14. Fewer of the white patients who used an IUD moved into a higher weight percentile category during their whole first treatment than either white patients

who used the combined tablet or Indian patients who used either treatment. Maximum weight change, though extremely variable, was a mean gain in all patients using the combined tablet, which increased progressively with longer treatment. The same trend, but less significant, was evident in the Indian patients who used an IUD; white patients who used an IUD, after an initial gain, tended to lose weight. Two factors may be involved:

A) a tendency for weight gain in some patients using the combined tablet,

B) white women may tend to be more weight conscious than Indian women.

15. Changes in blood pressure during the first viable pregnancy showed that more than 50% of white patients and even more Indian patients met the hypertensive criteria for toxemia. At least 60% of each race were under 20 yr. old at that time. The incidence of preeclampsia-eclampsia in this series as noted from hospital and clinic charts was 17% in the white patients and 28% in the Indian patients. It is evident that the hypertensive criteria set by the American Committee on Maternal Welfare were not used for chart diagnoses of toxemia of pregnancy.

16. The mean maximum weight gain during the first viable pregnancy did not differ significantly in either race from an average value of 24 lb. In white patients, there was some relation between interval weight gain (which probably reflected water retention) and maximum weight gain. Approximately 50% of patients of both races gained 3 lb. or more in any one week. This was about the same percentage of patients as fulfilled the hypertensive criteria for toxemia. This percentage far exceeds the incidence of toxemia of pregnancy quoted in standard textbooks of obstetrics.

17. Scores, based on the above analyses, were assigned to changes in blood pressure and weight during contraceptive treatment and during pregnancy. A large proportion of every group had scores which were not identical during pregnancy and during treatment for either or both parameters, a larger proportion scoring higher during pregnancies preceding the first treatment than during that treatment. Because of this, it was impossible to predict from the patient's behavior during pregnancy whether she would fulfil the criteria for blood pressure elevation during contraceptive treatment with the combined tablet.
18. In both contraceptive treatment groups an equal proportion of white patients had positive changes in weight and blood pressure; a larger proportion of Indian patients using the combined tablet had positive blood pressure than positive weight changes, but the reverse occurred in Indian patients who used an IUD. The reason for this observation is not apparent.
19. When the two parameters were compared in all pregnancies preceding the first treatment, a higher proportion had positive blood pressure than positive weight changes in all groups. Prenatal records were generally more complete for blood pressure than for weight.
20. Comparison of scores for patients who had two nonconsecutive courses of treatment with the combined tablet revealed that about the same number had positive changes during both courses of treatment for both blood pressure and weight. When patients changed from the combined tablet to an IUD, the same proportions had elevated pressures during both treatments, but fewer had significant weight gains when they used an IUD.

21. If it be accepted that rapid weight gains during pregnancy, during the normal menstrual cycle and during oral contraceptive therapy are caused by fluid retention which may reveal a sensitivity to hypertensive stimuli, it is clear from the present study that pregnancy favors this much more strongly than either endogenous or exogenous hormones in the nonpregnant state.

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APPENDIX A

5 mg

Each tablet contains: Active Ingredients—5 mg norethindrone (17 α-ethinyl-17-hydroxy-4-estren-3-one) and 0.075 mg mestranol (ethinyl estradiol 3-methyl ether).

Ortho-Novum

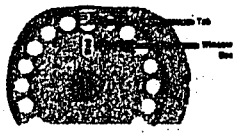
norethindrone with mestranol

20 Tablets **DIALPAK**
TRADEMARK

DOSAGE: One tablet daily as prescribed.

Each white tablet is engraved "ORTHO" one side; "V" on reverse.

Ortho Pharmaceutical (Canada) Ltd.
Don Mills, Ontario.



DIALPAK Tablet Dispenser
TRADEMARK

IMPORTANT—Read these directions thoroughly. Rotate the top clockwise until the day you take your first tablet appears in the window box. Example: If you take your first tablet on Wednesday, rotate the top clockwise until "WED" appears in the window box.

Now break off the tab marked "Lift Out" and remove the tablet which is exposed.

To dispense your tablet the following day, rotate the top clockwise so the next tablet is exposed.

Automatically the window box will always indicate the day on which the last tablet was taken.

Each white tablet contains: Active Ingredient—0.08 mg mestranol (ethinyl estradiol 3-methyl ether). Each blue tablet contains: Active Ingredients—0.08 mg mestranol (ethinyl estradiol 3-methyl ether) and 2 mg norethindrone (17α-ethinyl-17-hydroxy-4-estren-3-one).

Ortho-Novum SQ*

20 Tablets **DIALPAK***

DIALPAK* Tablet Dispenser

IMPORTANT—Read these directions thoroughly.

1. Note that there are 14 **white** tablets and 6 **blue** tablets. The tablets must be taken in the proper order, white tablets first.
2. Turn the top of the DIALPAK clockwise until the correct day of the week is opposite the **first** white tablet. (You may have to turn the top several times.)
3. Break off the "LIFT OUT" tab and remove the first white tablet. Next day turn the top to the next tablet.
4. Take one white tablet each day for 14 days, then take one blue tablet each day for 6 days.

Automatically the window box will always indicate the day on which the last tablet was taken.

*TRADEMARK

TABLET ADMINISTRATION CHART

Year	Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
	JANUARY																															
	FEBRUARY																															
	MARCH																															
	APRIL																															
	MAY																															
	JUNE																															
	JULY																															
	AUGUST																															
	SEPTEMBER																															
	OCTOBER																															
	NOVEMBER																															
	DECEMBER																															
	EXAMPLE			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓					

5 mg

Each tablet contains: Active Ingredients—5 mg norethindrone (17 α-ethinyl-17-hydroxy-4-estren-3-one) and 0.075 mg mestranol (ethinyl estradiol 3-methyl ether).

Ortho-Novum

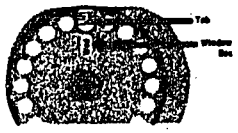
norethindrone with mestranol

20 Tablets **DIALPAK**
TRADEMARK

DOSAGE: One tablet daily as prescribed.

Each white tablet is engraved "ORTHO" one side; "V" on reverse.

Ortho Pharmaceutical (Canada) Ltd.
Don Mills, Ontario.



DIALPAK Tablet Dispenser
TRADEMARK

IMPORTANT—Read these directions thoroughly. Rotate the top clockwise until the day you take your first tablet appears in the window box. Example: If you take your first tablet on Wednesday, rotate the top clockwise until "WED" appears in the window box.

Now break off the tab marked "Lift Out" and remove the tablet which is exposed.

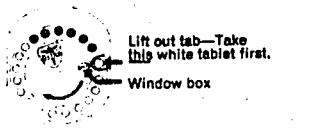
To dispense your tablet the following day, rotate the top clockwise so the next tablet is exposed.

Automatically the window box will always indicate the day on which the last tablet was taken.

Each white tablet contains: Active Ingredient—0.08 mg mestranol (ethinyl estradiol 3-methyl ether). Each blue tablet contains: Active Ingredients—0.08 mg mestranol (ethinyl estradiol 3-methyl ether) and 2 mg norethindrone (17α-ethinyl-17-hydroxy-4-estren-3-one).

Ortho-Novum SQ*

20 Tablets **DIALPAK***



DIALPAK* Tablet Dispenser

IMPORTANT—Read these directions thoroughly.

1. Note that there are 14 **white** tablets and 6 **blue** tablets. The tablets must be taken in the proper order, white tablets first.
2. Turn the top of the DIALPAK clockwise until the correct day of the week is opposite the **first** white tablet. (You may have to turn the top several times.)
3. Break off the "LIFT OUT" tab and remove the first white tablet. Next day turn the top to the next tablet.
4. Take one white tablet each day for 14 days, then take one blue tablet each day for 6 days.

Automatically the window box will always indicate the day on which the last tablet was taken.

*TRADEMARK

TABLET ADMINISTRATION CHART

Year	Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
	JANUARY																															
	FEBRUARY																															
	MARCH																															
	APRIL																															
	MAY																															
	JUNE																															
	JULY																															
	AUGUST																															
	SEPTEMBER																															
	OCTOBER																															
	NOVEMBER																															
	DECEMBER																															
	EXAMPLE			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓					

ORAL STUDY CLINICAL RECORD

Name or No:_____ Menarche (age)_____# of Pregnancies_____

Date:_____ Present Cycle:_____# of Children_____

Age:_____ Weight:_____ Last Delivery:_____# of Abcrtions_____

Indication:_____ Yrs. of Marriage:_____ Last Menses_____

Rx:_____mgm. of _____ Date_____ Rx Discontinued Date_____

Reason:_____

Physical Exam:_____

_____

CYCLE	DATE	WT.	DAYS OF CYCLE	DAYS OF MENSTRU-ATION	AMT. OF FLOW	DYSMEN-ORRHEA	BREAK-THROUGH	NAUSEA	LIBIDO	OTHER
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										

REMARKS:

RECORD LABORATORY DATA ON REVERSE SIDE

Return to: Clinical Research Dept., Ortho Pharmaceutical, Don Mills, Ontario.

ORAL CLINICAL RECORD - PATIENT

SURNAME _____ CHRISTIAN NAMES _____ NUMBER _____

CYCLE	MONTH OF BEGINNING PILLS	WEIGHT (DAY 5)	DATES PILLS TAKEN AND TOTAL NUMBER	DATES OF MENSTRUATION	*AMOUNT OF FLOW	*DYSMEN-ORRHOEA (PAIN)	**BLEEDING BETWEEN MENSES
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							

*
**
} See other side for instructions for these columns

INVESTIGATOR & CLINIC:

CLINICAL RECORD FORM
ORAL CONTRACEPTION

Rx ORF _____

FOR ORTHO USE ONLY
1. ORF: _____ (01-05)
2. INVESTIGATOR _____ (06-07)
3. PATIENT NO. _____ (08-10)

PATIENT'S NAME: _____ (SURNAME)

CASE OR RECORD NO.: _____

PATIENT HISTORY

4. DATE OF FIRST VISIT. [ ] [ ] [ ] (MO. DA YR.) 11-12
5. AGE. _____
6. WEIGHT. _____ 13-15
7. MENSTRUAL HISTORY:
   A. MENARCHE. _____ 16-17
   B. DAYS OF CYCLE. _____ 18-19
   C. DAYS OF FLOW. _____ 20
   D. AMOUNT OF FLOW: 21
   (1) LIGHT [ ] (2) MOD [ ] (3) HV [ ]
8. DATE LAST MENSES. [ ] [ ] [ ] (MO. DA YR.)
9. GRAVIDA. (NO. PREG.) _____ 22
10. ABORTIONS. _____ 23
11. PARA. (NO. DEL.) _____ 24
12. DATE LAST DELIVERY. [ ] [ ] [ ] (MO DA YR)

13. PAST HISTORY:

	NONE (0)	SLIGHT (1)	MOD. (2)	SEV. (3)	
DYSMENORRHEA	[ ]	[ ]	[ ]	[ ]	25
PREMENSTRUAL TENSION	[ ]	[ ]	[ ]	[ ]	26
MORNING SICKNESS	[ ]	[ ]	[ ]	[ ]	27
PHLEBITIS	[ ]	[ ]	[ ]	[ ]	28
OTHER DISEASE STATES AND SEVERITY	_____				29-30
	[ ]	[ ]	[ ]	[ ]	31

14. PREVIOUS ORAL CONTRACEPTIVE? (0) NO. [ ] (1) YES [ ] 32
IF YES, WHAT? _____ [ ] 33-34
DATE LAST TAKEN? [ ] [ ] [ ] (MO DA YR)

15. PHYSICAL EXAM. (0) NORMAL [ ] (1) OTHER [ ] 35
EXAM FINDINGS. _____ 36-37

DATE MEDICATION STARTED [ ] [ ] [ ] (MO DA YR)
QUANTITY GIVEN _____

CYCLE DATA

CYCLE NO.	DATE OF CONTACT	WT.	MENSES: DATE START OF FLOW	MENSES: NO. OF DAYS OF CYCLE	MENSES: NO. OF DAYS OF FLOW	MENSES: AMT. OF FLOW	MENSES: DYSMENORRHEA	MENSES: PREMENSTRUAL TENSION	SIDE EFFECTS: SPOTTING CYC. DAYS	SIDE EFFECTS: B.T.B. CYC. DAYS	SIDE EFFECTS: NAUSEA	SIDE EFFECTS: VOMITING	PERTINENT MED. COMPLAINTS AND REMARKS
38-39		40-42	43-44	45-46	47	48	49	50	51-52	53-54	55	56	57-58
						0 - NONE 1 - LIGHT 2 - MODERATE 3 - HEAVY OR SEVERE							
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													

PAP. SMEAR: CYCLE NO. (59-60) DATE CLASS (61)

	CYCLE NO. (59-60)	DATE	CLASS (61)
(1)	_____	[ ] [ ] [ ] (MO DA YR)	_____
(2)	_____	[ ] [ ] [ ] (MO DA YR)	_____
(3)	_____	[ ] [ ] [ ] (MO DA YR)	_____

ON CYCLE CARD NO.	CLASS
[ ]	[ ]
[ ]	[ ]
[ ]	[ ]

PLEASE ENTER LABORATORY AND EXAMINATION FINDINGS ON SEPARATE FORM.

DATE STOPPED THERAPY: [ ] [ ] [ ] (MO DA YR) 62-63
REASON: _____ 64-65

MAIL TO: DIVISION OF CLINICAL RESEARCH
ORTHO RESEARCH FOUNDATION
RARITAN, NEW JERSEY

INSTRUCTIONS:

1. The first day of menstruation is counted as Day 1.

2. Take one tablet daily from Day 5 until Day 25 (that is, 21 tablets).

3. If any bleeding begins before Day 26, take two tablets daily, and if this does not stop the bleeding within 3 days, telephone Doctor.

4. After Day 25, menstruation should begin within two to five days -- and if it does, count the first day of menstruation as Day 1 and repeat the course of treatment as before.

5. If menstruation has not begun by Day 32 (that is, 7 days after the last tablet was taken), count that day as Day 5 and begin taking the tablets as before.

   If you have taken the tablets as instructed, you have not become pregnant--an occasional period is skipped on this therapy and is not cause for any Concern.

6. Write down anything which seems different to you during the month indicated on the record space.

* 1. None
   2. Average (i.e. as before treatment)
   3. More than (as before treatment)
   4. Less than (as before treatment)

** Give dates and whether spotting or actual flowing.

Name_____ Age_____ Height_____ Para____

Menarche_____ Dysmenorrhoea_____

Cycle_____

Premenstrual and other symptoms_____

Obstetrical Difficulties_____

Date started O.N._____ Changes on Pills: Wt._____ Dysmenorrhoea

Flow_____ B.P._____ Other_____

Date	Cycle Day	Wt.	B.P.	Symptoms

APPENDIX B

C. P. D. Chart

Name

Pregnancy No.			
LNMP			
EDC			
Date 1st visit			
Past kidney infection			
Prepregnancy B.P.			
1st prenatal exam. B.P.			
- any lower B.P.			
- any > = 130/80			
- any S increase 30 mm. or D increase 15 mm.			
Weight - prepregnant			
- total gain			
- any gain > = 1 1/2 lb./wk. 3 lb. in 2 wks. 5 lb. in 1 mo.			
Edema			
Albuminuria			
Treatment - special diet			
- diuretic			
- Sat. visit			
- admission			
Kidney infection - positive urine culture			
- medications			
Discharge summaries - B.P.			
- diagnosis			
Miscellaneous symptoms			

ANTENATAL ADMISSIONS

Name	Chart		
Pregnancy No.			
LNMP			
EDC			
Admission date			
Length of stay			
Indication			
Diet			
Bed Rest			
Drugs - Diuretics			
Hypotensive			
Daytime Sedation			
$MgSO_4$			
Urinary			
Weight - initial			
- after 24 hr.			
- total change			
Edema - degree			
- change			
B.P. - frequency recorded			
- highest level			
- changes			
Albuminuria			
Hb			
Special iron			
Brisk reflexes			
Retina			
Miscellaneous symptoms			

Admissions for Delivery

Name	Chart No.		
Pregnancy No.			
LNMP			
EDC			
Date of admission			
Induction - reason			
B.P. in labor - any = > 130/80 and frequency			
Medications - $MgSO_4$			
- diurectics			
- hypotensives			
Brisk reflexes			
Examination of retina			
Mention of - abruptio placenta - placental infarcts - placental insufficiency			
Miscellaneous symptoms			
Post partum B.P. = > 130/80 - frequency of recordings			
Medications - diurectics - daytime sedation - $MgSO_4$ - hypotensives - for utinary tract infection			
Fever			
Anemia			
Hemorrhage			
Baby- sex weight apgar anomalies			

APPENDIX C

PILL PROGRAM

for Dr. Chernick

The main input data for this program is a set of about 12000 cards containing answers to a set of questions. The answers were obtained from questionnaires and patient's files. These cards all have a card number punched in columns 75-76 and subject number in 77-80.

For most questions the answers range from 1 to 9 and therefore 1 column is used for each such question. There are however some questions whose answers require two or three digits and therefore 2 or 3 columns are used for these questions. The basic problem or job was to count the subjects in each of a set of specified groups, the groups being determined by the answers to a specified set of questions

Example

Columns used to specify groups columns 8, 9, 10, 15, 16 each assumed to be a 1 column field with values ranging from 1-9. This would require 9x9x9x9x9 = 59,049 groups which exceeds the storage capacity of the machine (assuming 1 storage word for a counter/group). However since there were fewer than 1000 subjects not more than 1000 of these groups could contain members. Therefore the program operates as follows.

It reserves 800x12 storage words i.e. 1 set of 12 word/subject.

Then as each subject's data cards are read in the values punched in the specified columns are found and stored in one of these 12 words (maximum of 12 columns). The program then sorts these answers by columns in the sequence in which the columns are specified.

The program will print this table of answers before and after sorting if requested to do so.

After sorting the program begins comparing the answers given by each subject with the answers given by the previous (in the table) subject. As long as no difference is found for a particular column then a 1 is added to a counter for that column. When a difference is found in a particular column a 1 is added to the counters for all previous columns but not for the others. The program prints the values of all answers for the previous subject and then on the next line prints the word to be followed by the values of all counters. This printing takes place only when a difference is found. After printing, all counters, from the one containing the difference on to the last counter, are set to zero to begin counting a new group.

After completing this initial sort and counting, the program, if requested, will read in control cards causing the machine to resort the results and recount and print for as many control cards as specified. On completion of this, the program can begin all over by reading in the data again from tape along with necessary control cards and repeat the above for

some other columns.

A subroutine has been written which is intended to allow the program to delete some subjects as specified by another set of control cards. This subroutine is not yet incorporated into the program but probably will be this week (Nov. 13 - Nov. 19th) sometime.

APPENDIX D

APPENDIX D

SCORING OF PATIENTS USING THE SEQUENTIAL TABLET AS THE FIRST TREATMENT

Blood pressure and weight scores of 0, 1, and 2 were assigned to changes in these parameters occurring in patients using the sequential tablet as the first treatment (outlined in the Method). (Only white patients will be considered here as the small number of Indian patients in this category does not warrant analysis.) A significantly higher proportion of these patients had a score of 1 or 2 for blood pressure than for weight during the first treatment ($P < 0.02$). When all the pregnancies preceding this first treatment were considered, a higher proportion again appeared to have this score for blood pressure than for weight, but there were too few for the McNemar's analysis to be carried out. When each parameter scored was considered separately during this treatment and during the preceding pregnancies, significantly more patients scored 1 or 2 for the parameter during the pregnancies than during the sequential tablet treatment ($P < 0.01$) for both blood pressure and weight scores). When the combined score (see Method) was applied to the sequential tablet treatment and the preceding pregnancies, a significantly larger proportion scored 4, 5, or 6 during pregnancy than they did using the sequential tablet ($P < 0.001$).

For patients with two consecutive treatments who used the sequential tablet followed by the combined tablet, scores for each parameter were compared separately during the two treatments. A significantly higher proportion of patients

KEY TO APPENDIX D TABLE

Numbers lying along the diagonal line represent the number of patients whose score was the same for both parameters (blood pressure and weight) or whose score or combined score was the same in two situations (sequential tablet treatment and pregnancy or sequential tablet treatment and combined tablet treatment). For example, in Part 1A, 10 white patients had a blood pressure score of 0 and a weight score of 0 during treatment with the sequential tablet. For a perfect correlation of scores, all numbers would be on the diagonal line.

APPENDIX D TABLE

COMPARISON OF BLOOD PRESSURE AND WEIGHT SCORES

FOR PATIENTS USING THE SEQUENTIAL TABLET AS THE FIRST TREATMENT

Number of White Patients

1. Blood Pressure Vs. Weight Scores

A. During Seq. Tab. Treatment

Wt. Score \ B.P. Score	0	1	2
0	10	12	2
1	2	3	0
2	1	1	1

B. During Pregnancy

Wt. Score \ B.P. Score	0	1	2
0	1	3	4
1	2	8	8
2	0	2	5

2. B.P. Score Vs. B.P. Score during Seq. Tab.

during preg. \ during Seq. Tab.	0	1	2
0	2	1	0
1	6	5	1
2	5	10	2

Wt. Score Vs. Wt. Score during Seq. Tab.

during preg. \ during Seq. Tab.	0	1	2
0	5	2	1
1	13	3	2
2	6	0	0

3. Combined Scores for Blood Pressure and Weight Changes During Sequential Tablet Treatment and During Pregnancy.

Preg. Score \ Seq. Tab. Score	1	2	3	4	5	6
1	0	1	0	0	0	0
2	3	0	1	1	0	0
3	0	3	1	0	0	0
4	4	3	0	1	0	0
5	2	4	0	1	1	1
6	1	3	1	0	0	0

4. Two Consecutive Treatments - Seq. Tab. Followed by Comb. Tab.

B.P. Scores

Comb. Tab. \ Seq. Tab.	0	1	2
0	5	8	1
1	1	7	1
2	0	0	1

Weight Scores

Comb. Tab. \ Seq. Tab.	0	1	2
0	10	1	3
1	4	3	0
2	1	0	0

B.P. - blood pressure

Wt. - weight

Seq.Tab. - sequential tablet

Preg. - pregnancy

Comb. Tab. - combined tablet

scored 1 or 2 for blood pressure during the sequential tablet treatment than during the combined tablet treatment ($P < 0.05$). Patients were followed for fewer cycles during the second treatment; during the early months of the sequential tablet regime, follow-up visits were at monthly or bimonthly intervals whereas during combined tablet therapy, visits were only every three months. Consequently, the significantly higher proportion of patients with a score of 1 or 2 for blood pressure during the first treatment may reflect either a differential effect of the two regimes on blood pressure or simply be the result of the more numerous blood pressure recordings during the first treatment.

While McNemar's modification of the Chi Square could not be applied to the weight scores in the same way, a similar proportion appeared to have a score of 1 or 2 during both types of oral contraceptive treatment, indicating that some patients continued to gain weight following the change in medication. These weight gains may have been due to a similar effect exerted by both oral contraceptives or to a lack of motivation for personal weight control when the change in contraceptives was to yet another oral method.

APPENDIX E

BLOOD VOLUME STUDIES

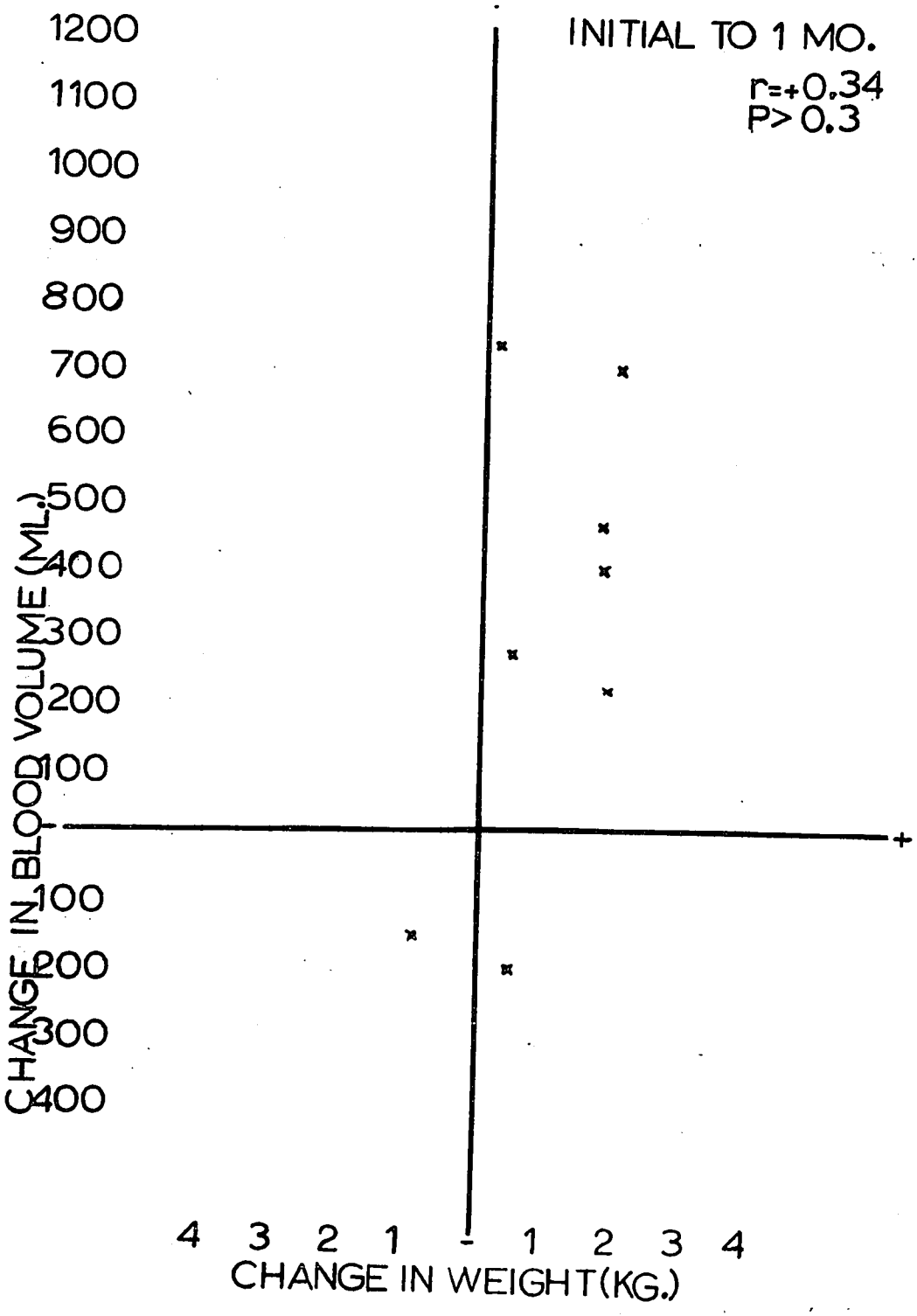
Blood volumes were measured with a RISA method by the Pathological Chemistry Department of Victoria Hospital on all new patients coming to the Clinic for contraception during one time period of this study. During this period, only one patient had an IUD inserted and so the remainder of the study was restricted to patients using the combined tablet. These determinations were performed at the initial visit to the Clinic, at one month of treatment, and at three months after the beginning of the contraceptive therapy.

Following the routine interviews and observations, the patient went to the laboratory where the plasma volume at 10 minutes after injection of the radioisotope was measured. The corrected hematocrit and the plasma volume were then used to calculate the blood volume. These volumes were analyzed to determine possible changes during the course of therapy and correlation of such changes with changes in body weight.

The weight change is plotted against the blood volume change from the initial estimation to that taken at one and three months in App. Figs. 1 and 2 respectively. There was essentially no difference in the mean values from one month to three months as shown in the accompanying table which presents the mean blood volume per body weight in ml./kg. for the group for each of the test times. The normal range for adults in that laboratory is 60 to 90 ml./kg. All mean values in our study fell within that range and there was no significant difference between them. Moreover, when mean changes were considered, there was no significant difference between the first and third readings or the second

APP. FIG. 1

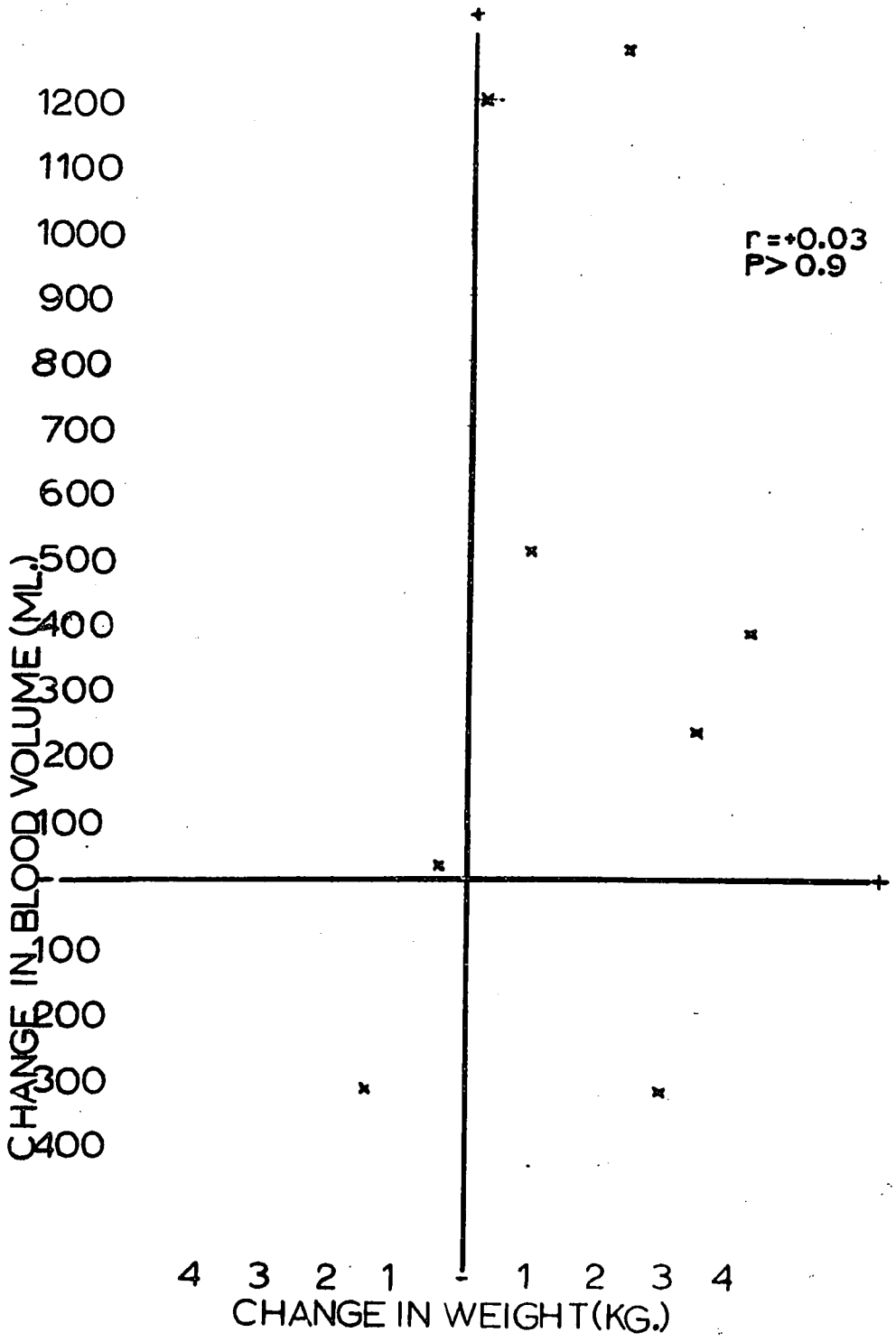
CORRELATION OF WEIGHT CHANGE
WITH BLOOD VOLUME CHANGE



APP. FIG. 2

CORRELATION OF WEIGHT CHANGE WITH BLOOD VOLUME CHANGE

Initial to 3 Mo.



and third readings but from the initial visit to the end of the first cycle the mean change approached significance. When changes in weight alone were considered, the changes in kilograms from the initial visit to the first month and to the third month were significant at the 5 percent level, while the change in weight from the first month to the third month approached significance. The correlation coefficient for the mean change in weight compared to the mean change in blood volume from the initial reading to the first month was + 0.34 ($P > 0.3$). When a similar analysis of the changes from the initial reading to the third month was considered, the correlation coefficient was + 0.03 ($P > 0.9$).

Time of Test	Blood Volume/Body Weight (ml./kg.) Mean ± S.D.
Initial	67.4 ± 10.13
1 mo.	71.1 ± 11.87
3 mo.	71.5 ± 9.27

Normal Range for Adults in Laboratory (60-90 ml./kg.)

Time Interval	Change in Blood Volume/Body Weight (ml./kg.) Mean	± S.D.	± S.E.M.	P
Initial-1 mo.	+3.7	± 5.35	± 1.891	> 0.05
Initial-3 mo.	+4.1	± 10.00	± 3.537	> 0.2
1 mo.-3 mo.	+0.5	± 10.05	± 3.553	> 0.9

Time Interval	Change in Weight (kg.) Mean	± S.D.	± S.E.M.	P
Initial-1 mo.	+1.0	± 1.10	± 0.388	< 0.05
Initial-3 mo.	+1.7	± 1.86	± 0.659	< 0.05
1 mo.-3 mo.	+0.7	± 0.97	± 0.342	> 0.05

Mean ± S.D. ± S.E.M. - Mean ± Standard Deviation ± Standard Error of the Mean

P - probability that the mean change is significantly different from the initial value

SKINFOLD MEASUREMENTS

Measurements of skinfolds were considered to be of possible value for the consideration of body composition and evaluation of weight change. Extensive skinfold measurements, using the Harpenden Skinfold Caliper, and trunk and limb circumferences, using a metal "circummeter"' were performed in a small group of patients (both Clinic and private). All of these women were using the combined tablet. They were each provided with a plasticized metric measuring tape and a Bathroom Scale which had been calibrated using five standard 20 lb. weights. They were asked to record at home their daily weight for a month as well as a small number of circumferences. A few jewellers' ring sizers were made available for daily measurement of the size of one finger.

Volunteers from a group of graduate nurses not using oral contraceptives were measured in the same way. In addition to the above observations, they were asked to record, daily, their blood pressure and basal body temperature as well as any subjective complaints referrable to the menstrual cycle, for up to five months.

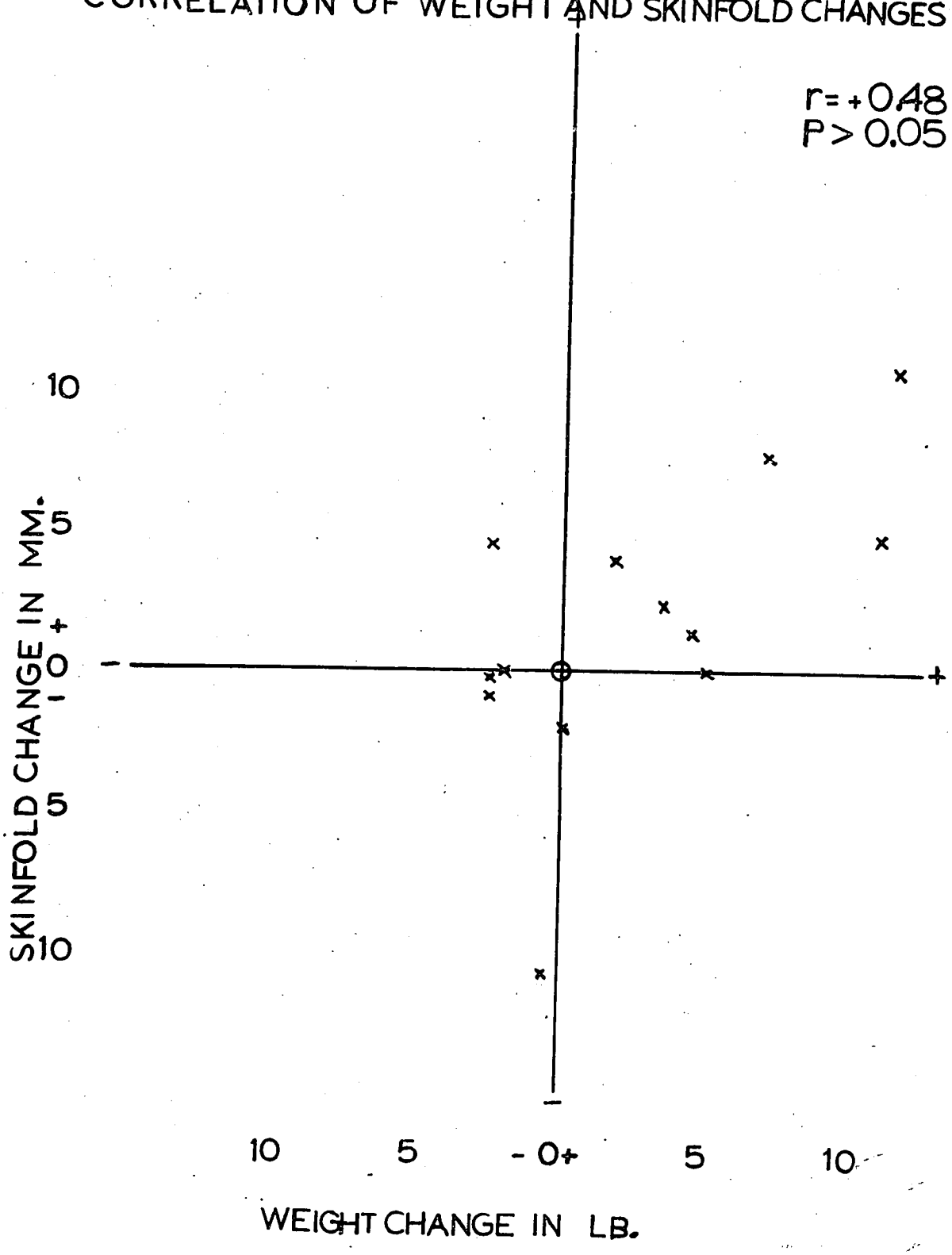
Volunteers from a group of student nurses also recorded menstrual data, daily weight, blood pressure and waist circumference.

Only the skinfold measured over the triceps of the Clinic patients was considered because tables of average values for Canadians were available for this variable (Pett and Ogilvie, 1957).

It was hoped to perform these at monthly intervals but some of the patients

APP. FIGURE 3

CORRELATION OF WEIGHT AND SKINFOLD CHANGES



did not return for up to three and a half months for their next supply of tablets and thus for their skinfold measurements. Only a few of the patients who had these measurements taken were starting the treatment at the time of the first set of readings. According to Pett and Ogilvie (1957) the skinfold measured over the triceps muscle is generally accepted as being a reliable measure of adiposity. App. Fig. 3 shows the weight change (lb.) plotted against this skinfold change (mm.) for the 13 patients who had repeat measurements. The correlation coefficient calculated for the mean changes in these parameters was +0.48 and this approached significance showing a tendency towards a positive correlation between skinfold change and weight change.

NAME _____ DATE _____

BIRTH DATE _____ HEIGHT _____ RELIGION _____

COUNTRY OF BIRTH _____ DATE OF IMMIGRATION _____

MENSTRUAL HISTORY _____

MENARCHE _____ CYCLE _____

_____

DYSMENORRHEA _____

_____

PREMENSTRUAL SYMPTOMS _____

_____

OVULATION SYMPTOMS _____

MARITAL STATUS _____ DATE OF MARRIAGE _____

OBSTETRICAL HISTORY _____ PARA _____

DATE	WEIGHT	LABOR	DELIVERY	COMPLICATIONS

METHODS TO PREVENT CONCEPTION _____

GENERAL HEALTH

MEDICAL _____

_____

SURGICAL _____

_____

REMARKS AND STUDY PARTICIPATION

Name_____ Age_____ Height_____ Class___

Menarche_____ Dysmenorrhoea _____

Cycle_____

_____

Premenstrual and other menstrual symptoms _____

_____

_____

NAME		
DATE		
CYCLE DAY		
CIRCUMFERENCES (CM.)		
Shoulders		
Chest a.		
b.		
Abdomen a.		
b.		
Buttocks -		
-		
Upper arm L		
R		
Forearm L		
R		
Wrist L		
R		
Thigh L		
R		
Knee L		
R		
Calf L		
R		
Ankle L		
R		
SKINFOLDS (MM.)		
Subscapular L		
R		
Lateral chest L		
R		
Triceps L		
R		
Biceps L		
R		
Iliac Crest L		
R		
Abdomen a.		
b.		
Anterior Thigh L		
R		
Posterior Thigh L		
R		
BREAST VOLUMES (L.)		
Left		
Right		

NAME ____________________

Date	Cycle Day	Time	Weight	Ring Size	Waist	Chest	Hips	L.Ankle	R.Ankle	Symptoms

APPENDIX TABLES

APPENDIX TABLE I

PERCENTAGE DISTRIBUTION OF THE NUMBER OF CYCLES COMPLETED DURING THE FIRST TREATMENT BY THE TYPE OF TREATMENT AND RACE

No. of Cycles	WHITE (N=465)		INDIAN (N=113)	
	Combined Tablet N=382	IUD N=83	Combined Tablet N=90	IUD N=23
0	14	29	12	5
1	6	16	8	17
2	5	9	8	9
3	6	2	7	4
4	6	7	3	4
5	6	7	1	13
6	5	2	6	0
7	5	6	2	4
8	3	4	1	4
9	3	2	5	9
10	2	5	2	9
11-15	9	6	7	18
16-20	7	4	8	4
21-25	7	1	8	0
26-30	5	0	4	0
31-35	4	0	4	0
36-40	2	0	7	0
41-45	2	0	1	0
46-50	1	0	4	0
51-60	2	0	1	0
61	0	0	1	0

N = number in group

APPENDIX TABLE IIa

PERCENTAGE DISTRIBUTION OF BLOOD PRESSURE CHANGES DURING THE FIRST TREATMENT EXCLUDING PATIENTS WHOSE INITIAL PRESSURE WAS ELEVATED OR NOT KNOWN

A. White Patients Using The Combined Tablet

Criteria	First 5 Cycles %	First 5 Cycles N	Second 5 Cycles %	Second 5 Cycles N	All Cycles Over 10 %	All Cycles Over 10 N
			After Initial			
S ≧ 140 once	%	214	7	138	7	102
S ≧ 140 > once	1	214	0	138	6	102
D ≧ 90 once	14	214	20	138	19	102
D ≧ 90 > once	2	214	1	138	19	102
S ≧ 140 and D ≧ 90	5	214	4	138	10	102
			Elevation From Initial			
S ≧ 30 once	23	214	4	138	7	102
S ≧ 30 > once	0	214	0	138	5	102
D ≧ 15 once	10	214	12	138	14	102
D ≧ 15 > once	2	214	4	138	21	102
S ≧ 30 and D ≧ 15	1	214	3	138	3	102
	S ≧ 140 or D ≧ 90		or inc. S ≧ 30		or inc. D ≧ 15	
once	18	214	23	138	17	102
> once	4	214	5	138	24	102
			Lowest to Highest Reading			
S > 30	2	214	4	138	14	102
D > 15	28	214	41	138	75	102
S > 30 and D > 15	1	214	4	138	14	102
			In Whole Treatment (Cycle Group Indicates No. Cycles Completed)			
	S ≧ 140 or D ≧ 90		or inc. S ≧ 30		or inc. D ≧ 15	
once	21	73	9	54	16	103
> once	3	73	9	54	39	103

N - no. in group
S - systolic blood pressure (mm.Hg)
D - diastolic blood pressure (mm.Hg)

APPENDIX TABLE IIb

PERCENTAGE DISTRIBUTION OF BLOOD PRESSURE CHANGES DURING THE FIRST TREATMENT EXCLUDING PATIENTS WHOSE INITIAL PRESSURE WAS ELEVATED OR NOT KNOWN

B. White Patients Using An IUD

Criteria	First 5 Cycles %	First 5 Cycles N	Second 5 Cycles %	Second 5 Cycles N	All Cycles Over 10 %	All Cycles Over 10 N
			After Initial			
S ≧ 140 once	3	36	0	15	0	6
S ≧ 140 > once	0	36	0	15	0	6
D ≧ 90 once	0	36	13	15	0	6
D ≧ 90 > once	0	36	7	15	0	6
S ≧ 140 and D ≧ 90	0	36	0	15	0	6
			Elevation From Initial			
S ≧ 30 once	3	36	7	15	0	6
S ≧ 30 > once	0	36	0	15	0	6
D ≧ 15 once	11	36	7	15	0	6
D ≧ 15 > once	0	36	7	15	0	6
S ≧ 30 and D ≧ 15	0	36	7	15	0	6
	S ≧ 140 or D ≧ 90 or inc.		S ≧ 30 or inc.		D ≧ 15	
once	14	36	13	15	0	6
> once	3	36	7	15	0	6
			Lowest to Highest Reading			
S > 30	0	36	7	15	33	6
D > 15	25	36	33	15	83	6
S > 30 and D > 15	0	36	7	15	33	6

	In Whole Treatment (Cycle Group Indicates No. Cycles Completed)					
	S ≧ 140 or D ≧ 90 or inc.		S ≧ 30 or inc.		D ≧ 15	
once	43	22	10	10	38	7
> once	0	22	20	10	0	7

N - no. in group
S - systolic blood pressure (mm.Hg)
D - diastolic blood pressure (mm.Hg)

APPENDIX TABLE IIc

PERCENTAGE DISTRIBUTION OF BLOOD PRESSURE CHANGES DURING THE FIRST TREATMENT EXCLUDING PATIENTS WHOSE INITIAL PRESSURE WAS ELEVATED OR NOT KNOWN

C. Indian Patients Using the Combined Tablet

Criteria	First 5 Cycles %	First 5 Cycles N	Second 5 Cycles %	Second 5 Cycles N	All Cycles Over 10 %	All Cycles Over 10 N
			After Initial			
S ≧ 140 once	11	44	3	31	29	24
S ≧ 140 > once	2	44	10	31	4	24
D ≧ 90 once	23	44	10	31	12	24
D ≧ 90 > once	2	44	13	31	27	24
S ≧ 140 and D ≧ 90	11	44	13	31	27	24
			Elevation From Initial			
S ≧ 30 once	2	44	0	31	12	24
S ≧ 30 > once	0	44	6	31	4	24
D ≧ 15 once	25	44	26	31	17	24
D ≧ 15 > once	7	44	6	31	29	24
S ≧ 30 and D ≧ 15	2	44	6	31	17	24
	S ≧ 140 or D ≧ 90		or inc. S ≧ 30		or inc. D ≧ 15	
once	30	44	16	31	12	24
> once	9	44	19	31	42	24
			Lowest to Highest Reading			
S > 30	0	44	10	31	42	24
D > 15	34	44	39	31	88	24
S > 30 and D > 15	0	44	3	31	38	24

	In Whole Treatment (Cycle Group Indicates No. Cycles Completed)					
	S ≧ 140 or D ≧ 90		or inc. S ≧ 30		or inc. D ≧ 15	
once	19	16	25	8	4	25
> once	12	16	0	8	60	25

N - no. in group
S - systolic blood pressure (mm.Hg)
D - diastolic blood pressure (mm.Hg)

APPENDIX TABLE IId

PERCENTAGE DISTRIBUTION OF BLOOD PRESSURE CHANGES DURING THE FIRST TREATMENT EXCLUDING PATIENTS WHOSE INITIAL PRESSURE WAS ELEVATED OR NOT KNOWN

D. Indian Patients Using An IUD

Criteria	First 5 Cycles %	First 5 Cycles N	Second 5 Cycles %	Second 5 Cycles N	All Cycles Over 10 %	All Cycles Over 10 N
After Initial						
S ≥ 140 once	0	10	0	7	0	3
S ≥ 140 > once	10	10	0	7	0	3
D ≥ 90 once	10	10	0	7	0	3
D ≥ 90 > once	10	10	0	7	0	3
S ≥ 140 and D ≥ 90	10	10	0	7	0	3
Elevation From Initial						
S ≥ 30 once	10	10	0	7	0	3
S ≥ 30 > once	0	10	0	7	0	3
D ≥ 15 once	10	10	0	7	0	3
D ≥ 15 > once	0	10	0	7	0	3
S ≥ 30 and D ≥ 15	0	10	0	7	0	3
	S ≥ 140 or D ≥ 90 or inc.		S ≥ 30 or inc.		D ≥ 15	
once	30	10	0	7	0	3
> once	10	10	0	7	0	3
Lowest to Highest Reading						
S > 30	0	10	0	7	0	3
D > 15	20	10	14	7	67	3
S > 30 and D > 15	0	10	0	7	0	3
In Whole Treatment (Cycle Group Indicates No. Cycles Completed)						
	S ≥ 140 or D ≥ 90 or inc.		S ≥ 30 or inc.		D ≥ 15	
once	40	5	0	5	33	3
> once	0	5	20	5	0	3

N - no. in group
S - systolic blood pressure (mm.Hg)
D - diastolic blood pressure (mm.Hg)

APPENDIX TABLE IIIa

PERCENTAGE DISTRIBUTION OF BLOOD PRESSURE CHANGES DURING THE FIRST VIABLE PREGNANCY RELATIVE TO THE TIME OF THE INITIAL READING

A. White Patients

Criteria	TIME OF INITIAL READING: Before 20 Wk. Gestation %	N	After 20 Wk. Before Labor %	N	During Delivery Hospital Admission %	N	Total %	N
				Initial				
S ≧ 140	5	42	6	67	15	97	10	206
D ≧ 90	2	42	6	67	27	97	15	206
S ≧ 140 and D ≧ 90	2	42	0	67	15	97	8	206
				After Initial				
S ≧ 140 once	12	42	15	67	15	97	15	206
S ≧ 140 > once	19	42	25	67	16	97	20	206
D ≧ 90 once	19	42	21	67	19	97	19	206
D ≧ 90 > once	38	42	42	67	28	97	34	206
S ≧ 140 and D ≧ 90	19	42	13	67	26	97	20	206
				Elevation From Initial				
S ≧ 30 once	0	41	15	65	9	70	9	176
S ≧ 30 > once	7	41	11	65	4	70	7	176
D ≧ 15 once	12	41	17	65	6	70	11	176
D ≧ 15 > once	54	41	43	65	20	70	36	176
S ≧ 30 and D ≧ 15	7	41	9	65	11	70	10	176
	S ≧ 140 or D ≧ 90 or inc. S ≧ 30 or inc. D ≧ 15							
once	14	42	13	67	24	97	18	206
> once	63	41	57	67	44	70	54	176
				Lowest to Highest Reading				
S > 30	49	41	43	65	36	70	41	176
D > 15	93	41	75	65	66	70	76	176
S > 30 and D > 15	49	41	15	65	31	70	30	176
				Highest Level After 20 Weeks				
S — 140-159	19	42	36	67	26	97	28	206
S = 160	10	42	6	67	10	97	9	206
D — 90-109	50	42	52	67	45	97	48	206
D = 109	7	42	11	67	6	97	8	206

N - no. in group
S - systolic blood pressure (mm.Hg)
D - diastolic blood pressure (mm.Hg)

APPENDIX TABLE IIIb

PERCENTAGE DISTRIBUTION OF BLOOD PRESSURE CHANGES

DURING THE FIRST VIABLE PREGNANCY RELATIVE

TO THE TIME OF THE INITIAL READING

B. Indian Patients

Criteria	TIME OF INITIAL READING: Before 20 Wk. Gestation %	N	After 20 Wk. Before Labor %	N	During Delivery Hospital Admission %	N	Total %	N
				Initial				
S ≧ 140	0	23	4	53	20	10	5	86
D ≧ 90	0	23	8	53	30	10	6	86
S ≧ 140 and D ≧ 90	0	23	4	53	20	10	5	86
				After Initial				
S ≧ 140 once	9	23	23	53	40	10	21	86
S ≧ 140 > once	26	23	36	53	20	10	31	86
D ≧ 90 once	17	23	25	53	30	10	23	86
D ≧ 90 > once	48	23	51	53	30	10	36	86
S ≧ 140 and D ≧ 90	35	23	55	53	40	10	48	86
				Elevation From Initial				
S ≧ 30 once	9	23	18	51	11	9	14	83
S ≧ 30 > once	17	23	25	51	0	9	20	83
D ≧ 15 once	13	23	25	51	0	9	19	83
D ≧ 15 > once	61	23	49	51	33	9	8	83
S ≧ 30 and D ≧ 15	22	23	38	51	11	9	31	83
	S ≧ 140 or D ≧ 90 or inc.		S ≧ 30 or inc. D ≧ 15					
once	13	23	24	53	44	10	23	86
> once	70	23	64	51	40	9	63	83
				Lowest to Highest Reading				
S > 30	48	23	53	51	22	9	48	83
D > 15	87	23	84	51	78	9	84	83
S > 30 and D > 15	48	23	53	51	22	9	48	83
				Highest Reading After 20 Weeks				
S — 140-159	31	23	40	51	40	10	37	86
S = 160	4	23	21	51	20	10	16	86
D — 90-109	61	23	59	51	40	10	59	86
D = 109	4	23	17	51	20	10	14	86

N - no. in group
S - systolic blood pressure (mm. Hg)
D - diastolic blood pressure (mm.Hg)

APPENDIX TABLE IVa

PERCENTAGE DISTRIBUTION OF BLOOD PRESSURE CHANGES

DURING THE FIRST VIABLE PREGNANCY IN PATIENTS

WITH AN ELEVATED INITIAL READING

A. White Patients —

Criteria	S ≧ 140 Or D ≧ 90				S ≧ 140 and D ≧ 90		Total	
	%	N	%	N	%	N	%	N
				After Initial				
S ≧ 140 once	20	5	7	15	25	16	17	36
S ≧ 140 > once	80	5	13	15	62	16	44	36
D ≧ 90 once	0	5	60	15	25	16	36	36
D ≧ 90 > once	40	5	33	15	56	16	44	36
S ≧ 140 and D ≧ 90	40	5	20	15	69	16	44	36
				Elevation From Initial				
S ≧ 30 once	0	4	0	10	0	13	0	27
S ≧ 30 > once	0	4	10	10	0	13	4	27
D ≧ 15 once	25	4	10	10	8	13	11	27
D ≧ 15 > once	50	4	10	10	0	13	11	27
S ≧ 30 and D ≧ 15	0	4	10	10	0	13	4	27
	S ≧ 140 or D ≧ 90 or inc. S ≧ 30 or inc. D ≧ 15							
once	25	5	54	15	25	16	36	36
> once	75	4	40	10	77	13	47	27
				Lowest To Highest Reading				
S > 30	50	4	10	10	85	13	52	27
D > 15	50	4	80	10	69	13	70	27
S > 30 and D > 15	50	4	10	10	69	13	44	27
				Highest Level After 20 Weeks				
S — 140-159	40	5	13	15	69	16	42	36
S ≧ 160	40	5	7	15	31	16	22	36
D — 90-109	40	5	93	15	81	16	81	36
D ≧ 109	20	5	7	15	19	16	14	36

N - no. in group
S - systolic blood pressure (mm.Hg)
D - diastolic blood pressure (mm.Hg)

APPENDIX TABLE IVb

PERCENTAGE DISTRIBUTION OF BLOOD PRESSURE CHANGES DURING THE FIRST VIABLE PREGNANCY IN PATIENTS WITH AN ELEVATED INITIAL READING

B. Indian Patients

Criteria	S ≧ 140 Or D ≧ 90				S ≧ 140 and D ≧ 90		Total	
	%	N	%	N	%	N	%	N
After Initial								
S ≧ 140 once	0	0	33	3	25	4	29	7
S ≧ 140 > once	0	0	33	3	75	4	57	7
D ≧ 90 once	0	0	33	3	25	4	29	7
D ≧ 90 > once	0	0	33	3	75	4	57	7
S ≧ 140 and D ≧ 90	0	0	33	3	100	4	71	7
Elevation From Initial								
S ≧ 30 once	0	0	0	3	67	3	33	6
S ≧ 30 > once	0	0	0	3	33	3	17	6
D ≧ 15 once	0	0	0	3	33	3	17	6
D ≧ 15 > once	0	0	33	3	33	3	17	6
S ≧ 30 and D ≧ 15	0	0	67	3	67	3	3	6
S ≧ 140 or D ≧ 90 or inc. S ≧ 30 or inc. D ≧ 15								
once	0	0	33	3	100	3	50	6
> once	0	0	67	3	100	3	67	6
Lowest To Highest Reading								
S > 30	0	0	0	3	100	3	50	6
D > 15	0	0	33	3	100	3	67	6
S > 30 and D > 15	0	0	0	3	100	3	50	6
Highest Level After 20 Weeks								
S — 140-159	0	0	33	3	25	4	29	7
S ≧ 160	0	0	0	3	75	4	43	7
D — 90-109	0	0	100	3	0	4	43	7
D ≧ 109	0	0	0	3	100	4	57	7

N - no. in group
S - systolic blood pressure (mm.Hg)
D - diastolic blood pressure (mm.Hg)

APPENDIX TABLE Va - WEIGHT

DISTRIBUTION OF MEAN HIGHEST AND LOWEST LEVELS RECORDED DURING EACH CYCLE GROUP OF THE FIRST TREATMENT EXPRESSED AS A CHANGE IN POUNDS FROM THE CONTROL WEIGHT ACCORDING TO THE INITIAL RATIO OF THE WEIGHT PERCENTILE TO THE HEIGHT PERCENTILE

a. White Patients Using Combined Tablet

Cycle Group	Ratio	Highest Weight Level (lb.) $\bar{X}$	S.D.	S.E.M.	N	P	Lowest Weight Level (lb.) $\bar{X}$	S.D.	S.E.M.	N	P
1st 5	< 1	+ 2.8	± 4.31	±0.417	107	< 0.001	-0.1	± 9.03	± 0.872	107	> 0.9
	1	+ 2.9	± 5.21	±0.716	53	< 0.001	+1.4	± 4.11	± 0.565	53	< 0.02
	>1	+ 2.1	± 5.86	±0.529	123	< 0.001	+0.2	± 5.82	± 0.525	123	> 0.7
	not known	+ 0.3	± 6.05	±1.677	13	> 0.8	-0.7	± 7.20	± 1.998	13	> 0.6
2nd 5	< 1	+ 4.6	± 7.81	±0.914	73	< 0.001	+3.3	± 6.29	± 0.736	73	< 0.001
	1	+ 6.9	± 8.07	±1.309	38	< 0.001	+5.7	± 7.70	± 1.249	38	< 0.001
	>1	+ 3.6	± 8.63	±0.904	91	< 0.001	+1.6	± 9.04	± 0.948	91	> 0.05
	not known	-0.2	± 8.02	±4.008	4	< 0.9	-1.0	± 6.63	± 3.317	4	> 0.7
10	< 1	+ 8.0	±10.00	±1.474	46	< 0.001	+2.4	± 8.21	± 1.211	46	> 0.05
	1	+ 9.8	±10.59	±2.077	26	< 0.001	+4.1	± 8.98	± 1.761	26	< 0.05
	>1	+10.5	±11.39	±1.342	72	< 0.001	+0.9	± 9.80	± 1.155	72	> 0.4
	not known	+ 1.6	± 7.92	±3.540	5	> 0.6	-9.2	±22.53	±10.077	5	> 0.4

Ratio - Initial Weight Percentile:Height Percentile

$\bar{X}$ ± S.D. ± S.E.M. - Mean ± Standard Deviation ± Standard Error of the Mean

N - number in group

P - probability that the weight change is significantly different from the initial value

APPENDIX TABLE Vb - WEIGHT

DISTRIBUTION OF MEAN HIGHEST AND LOWEST LEVELS RECORDED DURING EACH CYCLE GROUP OF THE FIRST TREATMENT EXPRESSED AS A CHANGE IN POUNDS FROM THE CONTROL WEIGHT ACCORDING TO THE INITIAL RATIO OF THE WEIGHT PERCENTILE TO THE HEIGHT PERCENTILE

b. White Patients Using An IUD

Cycle Group	Ratio	Highest Weight Level (lb.) $\bar{X}$	S.D.	S.E.M.	N	P	Lowest Weight Level (lb.) $\bar{X}$	S.D.	S.E.M.	N	P
1st 5	< 1	- 1.2	± 2.80	±0.775	13	> 0.1	-1.9	± 2.84	±0.789	13	< 0.05
	1	+ 1.4	± 5.95	±2.104	8	> 0.5	+0.4	± 6.16	±2.179	8	> 0.8
	>1	+ 2.2	± 7.08	±1.582	20	> 0.1	+0.8	± 7.25	±1.621	20	> 0.6
	not known	+ 6.2	± 7.08	±1.965	13	< 0.01	+3.5	± 6.59	±1.828	13	> 0.05
2nd 5	< 1	- 4.3	± 5.22	±1.973	7	> 0.05	-4.9	± 5.01	±1.895	7	< 0.05
	1	+ 2.2	± 4.82	±2.150	5	> 0.3	+1.8	± 4.49	±2.010	5	> 0.4
	>1	+ 2.9	±11.38	±3.155	13	> 0.3	+1.8	±11.34	±3.146	13	> 0.5
	not known	+10.0	± 2.00	±1.155	3	< 0.02	+8.7	± 1.16	±0.668	3	< 0.01
10	< 1	- 2.2	± 6.45	±3.224	4	> 0.5	-3.2	± 7.27	±3.637	4	> 0.4
	1	+ 1.5	± 0.71	±0.500	2	> 0.2	+1.5	± 0.71	±0.500	2	> 0.8
	>1	+ 4.6	±15.80	±7.068	5	> 0.5	-9.4	± 9.42	±4.214	5	> 0.1
	not known	+17.0			1		+17.0			1	

Ratio - Initial Weight Percentile:Height Percentile
$\bar{X}$ ± S.D. ± S.E.M. - Mean ± Standard Deviation ± Standard Error of the Mean
N - number in group
P - probability that the weight change is significantly different from the initial value.

APPENDIX TABLE Vc - WEIGHT

DISTRIBUTION OF MEAN HIGHEST AND LOWEST LEVELS RECORDED DURING EACH CYCLE GROUP OF THE FIRST TREATMENT EXPRESSED AS A CHANGE IN POUNDS FROM THE CONTROL WEIGHT ACCORDING TO THE INITIAL RATIO OF THE WEIGHT PERCENTILE TO THE HEIGHT PERCENTILE

c. Indian Patients Using the Combined Tablet

Cycle Group	Ratio	Highest Weight Level (lb.) $\bar{X}$	S.D.	S.E.M.	N	P	Lowest Weight Level (lb.) $\bar{X}$	S.D.	S.E.M.	N	P
1st 5	< 1	+ 3.0	±2.45	±1.225	4	> 0.05	+2.2	±1.71	±0.854	4	> 0.05
	1	+ 5.5	±7.67	±2.712	8	> 0.05	+3.9	±8.41	±2.973	8	> 0.2
	> 1	+ 3.9	±3.74	±0.517	47	< 0.001	+2.3	±4.13	±0.603	47	< 0.001
	not known	+ 1.6	±1.67	±0.748	5	> 0.05	+2.2	±2.49	±1.114	5	> 0.1
2nd 5	< 1	+ 7.0	±5.66	±4.000	2	> 0.3	+6.5	±4.95	±3.500	2	> 0.3
	1	+ 1.8	±3.90	±1.743	5	> 0.3	+1.4	±3.97	±1.778	5	> 0.4
	> 1	+ 5.3	±6.35	±0.991	41	< 0.001	+3.4	±6.35	±0.992	41	< 0.01
	not known	+ 6.0			1		+5.0			1	
> 10	< 1	+17.5	±7.78	±5.590	2	> 0.1	+6.0	±7.07	±5.000	2	> 0.4
	1	+15.0	±8.66	±5.000	3	> 0.05	-2.0	±12.49	±7.211	3	> 0.7
	> 1	+12.0	±8.65	±1.530	32	< 0.001	+1.2	±9.50	±1.679	32	> 0.4
	not known	+ 5.0			1		+5.0			1	

Ratio - Initial Weight Percentile:Height Percentile

$\bar{X}$ ± S.D. ± S.E.M. - Mean ± Standard Deviation ± Standard Error of the Mean

N - number in group

P - probability that the weight change is significantly different from the initial value

APPENDIX TABLE Vd - WEIGHT

DISTRIBUTION OF MEAN HIGHEST AND LOWEST LEVELS RECORDED DURING EACH CYCLE GROUP OF THE FIRST TREATMENT EXPRESSED AS A CHANGE IN POUNDS FROM THE CONTROL WEIGHT ACCORDING TO THE INITIAL RATIO OF THE WEIGHT PERCENTILE TO THE HEIGHT PERCENTILE

d. Indian Patients Using An IUD

Cycle Group	Ratio	Highest Weight Level (lb.) $\bar{X}$	S.D.	S.E.M.	N	P	Lowest Weight Level (lb.) $\bar{X}$	S.D.	S.E.M.	N	P
1st 5	< 1	+ 1.7	± 2.52	±1.454	3	> 0.3	+ 1.7	± 2.52	±1.454	3	> 0.3
	1	0			1		0			1	
	> 1	+ 3.2	± 6.19	±1.787	12	> 0.1	+ 0.4	± 5.92	±1.708	12	> 0.8
	not known	+12.67	± 4.62	±2.667	3	< 0.05	+10.6	± 7.02	±4.055	3	> 0.1
2nd 5	< 1	- 2.5	±13.44	±9.500	2	> 0.8	- 2.5	±13.44	±9.500	2	> 0.8
	1	+ 5.0			1		+ 3.0			1	
	> 1	+10.8	±10.99	±4.913	5	> 0.05	+ 8.6	± 9.97	±4.456	5	> 0.1
	not known	+16.5	±13.44	±9.500	2	< 0.3	+16.5	±13.44	±9.500	2	> 0.3
10	< 1				0					0	
	1	+ 8.0			1		+ 8.0			1	
	> 1	+17.3	± 7.51	±4.334	3	> 0.05	+14.3	± 9.29	±5.365	3	> 0.1
	not known	+14.0			1		+14.0			1	

Ratio - Initial Weight Percentile:Height Percentile
$\bar{X}$ ± S.D. ± S.E.M. - Mean ± Standard Deviation ± Standard Error of the Mean
N - number in group
P - probability that the weight change is significantly different from the initial value