ON THE HISTORY OF HORMONAL CONTRACEPTION II. OTFRIED OTTO FELLNER (1873-19??) AND ESTROGENS AS ANTIFERTILITY HORMONES.

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ABSTRACT

Otfried Otto Fellner was a pioneer in gonadal endocrinology. In 1922, he reported briefly that he had rendered animals infertile by injecting estrogenic extracts of ovaries and placenta, thus confirming Haberlandt's concept of hormonal sterilization. In 1927, similar observations were reported by Leo Loeb, who used follicular extracts. That same year Fellner published a more detailed report of his findings and proposed two hypotheses: 1. "Feminin" (Fellner's term for his estrogenic material) in large doses causes sterility by damaging the egg. 2. The effect of "Feminin" differs according to the dose given. Only when administered in very large quantities will it suppress ovulation. Both hypotheses (though mainly based on intuition) were shown to be valid when pure estrogens became available for experimental use during the 1930's. Experiments of that time demonstrated that the suppressive action of estrogens on ovulation was mediated by the pituitary. It was also found during the 1930's that estrogens in large quantities interfere with tubal and uterine egg transport and with the action of progesterone upon the endometrium. These findings both confirmed and extended Haberlandt's concept of hormonal sterilization.

INTRODUCTION

In his incomplete and unpublished autobiography (1) Ludwig Haberlandt (2) wrote late in 1921: "In November, I presented my new method [ovarian transplantation for hormonal contraception] to the Medical Society of Innsbruck. The presentation aroused great interest; I might even say, that it caused a sensation. The matter is, of course, both so surprisingly new and so simple

that several people called it a 'Columbus' egg'"(3). In March, 1922, the meeting of the Deutsche Gesellschaft für Gynäkologie was held in Innsbruck. Of that meeting Haberlandt wrote: "I was able to discuss my transplantation experiments with the most eminent specialists who, to my sincere gratification, expressed great interest ..." (4).

During the 1922 meeting, following a presentation by Bernard Zondek (1891-1968), Haberlandt spoke only briefly about his experiments discussing the problem of testing the specifity of "Optone" (2) and reporting that he had achieved a temporary sterilization by suppression of ovulation through ovarian transplants (5). If Zondek made any comment on this, it was not recorded. We do not know whether Haberlandt was in the audience when later at the same meeting Otfried Otto Fellner (1873-19??) of Vienna discussed a paper on superfetation and questioned the occurrence of ovulation during pregnancy. Haberlandt's experiments and his own, Fellner pointed out, made such ovulation unlikely: "After injection of the female sexual lipoid, the active substance of corpus luteum and placenta, animals remain sterile for several months. This confirms similar experiments by Haberlandt" (6).

Fellner's discussion is noteworthy for two reasons. Firstly, it marked the earliest public acknowledgement and confirmation of Haberlandt's work. Second, in his discussion, Fellner also became the first person to suggest that estrogens can cause infertility. Later Haberlandt gratefully mentioned Fellner's "friendly communication of unpublished results" (7,8); and in 1927, when Fellner presented his most recent findings in some detail (9), he stressed that he had confirmed Haberlandt's statements as early as 1922 (10).

Fellner's concepts, his work in the later 1920's and his dispute with Haberlandt are the subjects of this paper.

OTFRIED OTTO FELLNER'S EARLY STUDIES

Fellner was born in Vienna on September 20, 1873, son of the Jewish physician Leopold Fellner and his wife Emilie (11,12). He received his secondary school education at the academic Gymnasium in Vienna and graduated on July 7, 1892 (13). In the fall of 1892, he began the study of medicine in Vienna (14). In the latter part of his medical education, during the winter of 1895-1896 he attended the gynecological and obstetrical lectures of Rudolf Chrobak (1843-1910). Chrobak had just induced his assistant Emil Knauer (1867-1935) to undertake ovarian transplants. The following summer, Fellner enrolled for the lectures of Friedrich Schauta (1849-1919). It was in Schauta's Klinik that Josef Halban (1870-1937) was soon to conduct ovarian transplants and to deduce from the results of these experiments the endocrine function of the ovary.

Fellner does not seem to have been an outstanding student. He passed all his examinations, but was graded only as fair. On November 11, 1898, he was awarded the M.D. degree (13). Fellner took his training in Obstetrics and Gynecology at the Bettina Pavillon, a private hospital in Vienna, and at the I. Frauenklinik of Schauta, also in Vienna. For four years Fellner was Operationszögling (in effect intern and resident) under Schauta (12). Though he did not become an assistant, he nonetheless was a student of Schauta's at a time when through Halban's efforts endocrinology reached a peak at the I. Frauenklinik. Though Fellner's studies were to contribute greatly to the understanding of the endocrinology of reproduction, he did not achieve an academic appointment, but went into private practice. In his spare time, however, he performed many basic studies working mainly at the Institut für allgemeine und experimentelle Pathologie of the University of Vienna.

It is probable that Schauta and Halban were responsible for interesting Fellner, but credit for stimulating him to undertake his pioneering studies just prior to World War I goes to Artur Biedl (1869-1933) then Professor at the above mentioned pathological institute. To Biedl, Fellner later expressed his thanks for supervision and guidance (15).

It should be remembered that it was Biedl, who in 1910, published the first major review on endocrinology (16); that is now considered a classic. His influence on Fellner, and thus on early studies of reproductive endocrinology has not previously been recognized. Biedl left for Prague in 1913, but Fellner continued at the Institute for General and Experimental Pathology. As late as 1935, his papers were published under its auspices.

In spite of all his experimental work, Fellner was never recognized by the University, even to the extent of becoming Privatdozent. Among distinguished Viennese gynecologists who did not succeed in having academic careers, Fellner appears to have been the most unfortunate, certainly more so than Halban, who eventually received a professorship though never a chair (17). During the 1930's Fellner was listed as a gynecologist in Vienna (11,12,18). As late as 1933, he addressed the Gesellschaft der Ärzte in Vienna (19). In 1936, he was hailed as one of the best known and most popular gynecologists in Vienna (20). These are the last reports of him. No obituary can be found.

Before he confirmed Haberlandt's work, Fellner achieved remarkable results in his own scientific endeavors, results which led him eventually to his contributions to the concept of hormonal contraception. Most of his work dealt with gonadal and placental endocrine function. He was among the first ones to study the effects of X-rays upon the histological features of the ovaries (21,22). Histological studies of human ovaries obtained during various stages of pregnancy followed (23,24,25). Fellner concluded

that during pregnancy both ripening of follicles and ovulation are suppressed, but endocrine function (as judged by the appearance of interstitial cells) is increased. Much later, in 1921, Fellner reported that injection of extracts from interstitial tissue of pregnant cows' ovaries had indeed a considerable effect upon the uterus (26). Haberlandt considered this finding as support for the concept that interstitial cells function during pregnancy like corpora lutea - a concept which played a major role in his early experimental work (27). Haberlandt did not recognize that the effects reported by Fellner were due to estrogens (28). In 1922, however, the roles of ovarian and placental tissues in hormonal secretion had not been defined. No one knew, for instance, how many hormones were secreted by which organ, or whether within the ovary the corpus luteum, the follicle, or both produced the same hormone or different hormones.

As early as 1912, Fellner had reported that residues of alcohol and other extracts of human placentae suspended in saline solution and injected into intact and castrated immature rabbits stimulated growth of uterus, vaginal epithelium and breasts (15). In an extensive presentation a year later he also reported on the effects of extracts from corpora lutea (29). Fellner's use of placental extracts provided the first experimental confirmation of Halban's hypothesis of endocrine placental function (17). Fellner's work was further important from a methodological point of view. As George W. Corner (b.1889) discussed (30), Fellner was among the first investigators to use organic solvents to extract ovarian and placental tissues and thus succeeded in producing potent ovarian and placental extracts. None of the early investigators studied the effects of such extracts upon fertility. However, statements were made as to changes in ovaries after treatment. Fellner's observations were inconclusive: the size of his animal's ovaries varied from undersized to enlarged. Henri Iscovesco (1859-19??) who worked in Paris at the Laboratoire de Physiologie de la Sorbonne gave the first reports on active ovarian lipoid extracts in 1912 (31-36); he found that the ovaries of rabbits and other animals became enlarged and rich in follicles after injection of organic extracts of cow, mare and sow ovaries (32). However, when Iscovesco injected extracts of corpora lutea the ovaries became smaller (33). These findings might be considered to support the Beard-Prenant hypothesis (2), but Iscovesco did not draw this conclusion. Admittedly the original evaluations of ovarian changes by Fellner and Iscovesco were crude, and neither author was concerned with ovulation and conception. Fellner's attitude changed in the early 1920's. It appears that he was the first one to recognize that estrogens given in large doses can cause infertility.

FELLNER'S EXPERIMENTS AND HIS CONCEPT OF HORMONAL STERILIZATION

The results of the experiments which Fellner reported on briefly in 1922 (6) were never published in detail. Interestingly, in an extensive paper published in 1921, Fellner had observed

that testicular size in male animals was reduced by placental and ovarian extracts (37). After much improvement of his extraction procedure (38), Fellner repeated the experiments in female animals in 1926 and 1927. His findings and conclusions were presented at length on June 3, 1927 to the Gesellschaft der Ärzte in Vienna. An abstract appeared in the Wiener Klinische Wochenschrift (39). The extensive paper was published in the Medizinische Klinik in October, 1927 (9). In essence, Fellner's experiments confirmed the possibility of hormonal sterilization, but he differed from Haberlandt by arriving at a new interpretation of the mechanism of such sterilization.

First of all, Fellner refuted some of Haberlandt's critics. Several investigators had claimed that Haberlandt was dealing with non-specific effects of his protein containing extracts. Fellner now pointed out that his purified material did not contain any proteins and yet produced sterility (40). Another criticism was based on the consideration that animals which had been injected several times daily, could well have been in too much distress to allow coitus. Fellner stated that he had usually given only one injection to achieve sterility for several days. We might add that Haberlandt also had not achieved sterility when he injected extracts from ovaries of nonpregnant animals (41). In any case, Haberlandt's feeding experiments further contraindicated toxic effects. Fellner also added that he let his own animals drink a solution of "Feminin" (as he called his estrogenic material) and thereby induced sterility. All in all, by argument and experiment Fellner supported Haberlandt's concept of a specific hormonal sterilization.

Fellner, incidentally, claimed that when Haberlandt conducted his feeding experiments he was following Fellner's example (42). This claim to priority was not justified by the facts. Admittedly, Fellner had reported in 1925 on oral application of his extracts (43). He had used this route to study hormonal effects upon experimental cancer in mice. By then, however, Haberlandt had already been carrying out feeding experiments for some time. He had actually started such experiments as early as the summer of 1923, if not earlier (44). Later, he did not dispute Fellner's claim. Perhaps Haberlandt realized that neither could claim the first oral use of gonadal extracts. They had been in vogue in clinical gynecology since 1895. In fact, it was dissatisfaction with such oral applications that led Rudolf Chrobak in 1895 to urge his assistant Knauer to transplant ovaries (45).

When Fellner treated 15 guinea pigs with "Feminin", none became pregnant. Out of 30 treated rabbits, only 3 conceived, as did 3 out of 100 mice. Almost all the offspring of the "failures" were females. Two rabbits did not conceive, but behaved as in pseudopregnancy. They built nests, for example, though incompletely. One of the animals showed several corpora lutea at autopsy. On the basis of this single observation Fellner concluded that the female hormone did not interfere with

ripening of the follicle and ovulation, but damaged the egg directly. "If one bases hormonal sterilization not on Beard's theory [sic] but the concept that Feminin damages primarily the eggs... all findings mentioned above can be explained without strain" (46).

Fellner did not provide histological proof that estrogens damage the egg. The basis for his conclusion was very shaky indeed. Why did so few animals go into pseudopregnancy? What were the ovarian findings in the many animals which did not become pregnant or pseudopregnant? Fellner promised more experiments, but as far as can be determined, he never published on them, if indeed they were ever carried out. His conclusion, then, about the hormonal influence upon the egg (rather than upon the follicle and ovulation) was derived from intuition and not from solid experimentation.

It was also more by intuition than experimentation that Fellner ascribed to "Feminin" (and thus to estrogen) different activities dependent upon the size of the administered dose. His summary merits translation: "With increasing doses of Feminin, one can obtain different results on animals:

1. Estrus, enlargement of the uterus
2. Fewer and predominantly female offsprings.
3. Destruction of the eggs without inhibition of corpus luteum formation. Hormonal sterilization (building of a nest without pregnancy)
4. Destruction of eggs, with inhibition of corpus luteum formation. No pregnancy (no building of nest)" (47).

The last would eventually lead to lasting sterility for which Fellner coined the term "hormonal castration". As to his second point, it should be added that other investigators were unable to influence the sex of offspring by giving hormones.

According to Fellner, then, the same hormone could be either beneficial or detrimental, depending upon the quantity administered. It was not necessary to postulate a specific inhibitory hormone. Here, Fellner, was soon shown to be wrong as were many others. In 1927, he did not recognize that a pharmacological effect of estrogen did not rule out the existence of a second different hormone. Nonetheless, in another publication in 1927, in an obscure journal (48) he once more emphasized quite correctly, that estrogens had different effects depending upon the amounts given. He stated that although it appeared paradoxical for the same hormone to both cure and cause sterility, this was only a question of dosage (49).

In essence then, Fellner demonstrated the antifertility action of purified estrogen containing extracts. He postulated that

ovarian hormones (as well as placental hormones) in large doses interfere with their main purpose, i.e. the support of eggs. He stated that, in general, estrogens act differently dependent upon the size of the dose given.

ESTROGENS AS ANTIFERTILITY HORMONES

To put Fellner's work and hypotheses into proper perspective, it becomes necessary to discuss the studies which preceded his and to review the later development, which proved him to be correct.

As mentioned earlier, the effects of ovarian extracts upon the ovaries of test animals had been studied by Fellner and Iscovesco as early as 1912. Neither investigator was at that time interested in the contraceptive action of ovarian extracts; they only observed gross changes in ovaries in response to such extracts. Their observations actually did not allow any conclusion as to enhanced or impeded fertility. The inconsistent changes of ovarian size observed by Fellner (29) or the enlargement of ovaries with follicular development seen by Iscovesco (32) were remarkable, but nothing more. Another study of 1912 which gave more information but was later forgotten was that of Ludwig Adler (1876-19??). Adler, also an assistant of Schauta's in Vienna, had earlier collaborated with Fritz Hitschmann (1869-1926) in what are now considered classic studies of the endometrium (50,51). In 1912, Adler reported that water extracts of ovaries hastened follicular ripening, which was then followed by degeneration of egg and follicle (52). As a rule, corpora lutea were not found. No observation as to fertility was recorded, nor was it concluded that these ovarian changes would make procreation impossible. Adler's findings were buried in a paper on many subjects, as were the confirmatory observations of Bernard Aschner (1883-1960) (53). Later investigators also may have neglected Adler and Aschner because of their use of watery extracts. Although lipoid solvents were of great importance in isolating estrogens, it was eventually established that these hormones are also soluble in water, though much less so.

The early studies, as mentioned, were not aimed at demonstrating an antifertility action of ovarian hormones; ovarian changes observed were not consistent; and finally, the extracts used did not contain only estrogens as particularly apparent from the study of Edmund Herrmann (1875-1930) (54). This criticism also applies more or less to the studies conducted by various investigators during the 1920's. The water soluble "Folliculin" which Bernard and Selmar Aschheim (1875-1965) used did not contain progesterone, but included substances other than estrogens (55). On the other hand, the lipoid extracts of follicles or follicular fluid used by others contained mainly estrogens, although other substances were also present, including small amounts of progesterone.

The same criticism applies to the studies of Leo Loeb (1869-1959) and William B. Kountz (1896-1962). Loeb's contributions to the elucidation of the corpus luteum have been mentioned previously (2). In 1927, when at the Department of Pathology of Washington University School of Medicine, St. Louis, Loeb and Kountz finished a study on the effects of follicular extracts upon guinea pigs (56,57). When they studied the action of the corpus luteum upon the alleged ovulation-stimulation effect of follicular hormone, they found an inhibitory effect instead: "...to our surprise we found in the course of our investigations that the injections of follicular extract, instead of calling forth ovulation in the guinea pig, on the contrary prevented it and thus led to a sterile condition of the animal during the time that the injections were effective" (58). Only one animal which had received a smaller dose of extract, ovulated (59). This experiment might have provided a clue as to the physiological and pharmacological effects of follicular hormone; but Loeb had not yet encountered Fellner's hypothesis and did not look upon the different results as being caused by different quantities of the same hormone. He speculated, rather, about the discrepancy between the normal effects of follicular hormone early in the cycle and the suppression of ovulation observed after injection of follicular extracts: "This effect of the injections is not analogous to the action of the follicular substance in the normal animal; it must be due either to the abnormal mode of administration of the extract, to a substance admixed to it, or possibly to the lack of sufficient absorption of the follicular substance in the normal animal at the time of oestrus or preceding it" (60). During the following decade it was to be shown that none of these explanations was correct. Nevertheless, Loeb found simultaneously and independently of Fellner that an estrogen containing extract can interfere with fertility. Because of the origin of Loeb's extracts (i.e. follicles) it may be assumed that he was working with purer estrogen than was Fellner whose extracts were obtained mainly from placentae.

In 1927, the question of one ovarian hormone versus two hormones (i.e. estrogen and gestagen) was not yet settled: Haberlandt's writings around that time (partially in response to Fellner) reflect this uncertainty quite well. Early in 1928, Haberlandt gave a lecture on hormonal sterilization in Innsbruck and another in Vienna (61). In discussing sources of the inhibitory hormone, he referred to the recent discovery that the urine of pregnant females was such a source. The urine, as Aschheim and Zondek had reported the previous year from the Universitäts-Frauenklinik at the Charité in Berlin, contained large amounts of estrogenic hormone (62,63). When he mentioned this discovery, Haberlandt apparently did not distinguish the inhibitory from the stimulatory hormone, though all his previous work had been based on the concept of a specific

ovulation-inhibiting hormone, nor did he refer to Fellner's paper in the Medizinische Klinik (9). It did not take Fellner long to bring his publication to Haberlandt's attention. In a short note, Fellner repeated his hypothesis: "The capacity to sterilize is not related to an inhibitory substance, but to Feminin" (64).

Haberlandt responded to Fellner in a subsequent note (65); but his answer did not clarify the matter. In his noble way he did not mention that he had briefly discussed Fellner's paper of 1927 elsewhere that very same year (66). He stressed that inhibition of ovulation had been demonstrated many times by himself and others. He apparently implied that Fellner's postulate of a direct action upon the egg, had an insufficient basis. On the other hand, by referring again to the urine of pregnant women, he admitted the possibility that estrogens might act as contraceptive agents. In subsequent publications, in 1931, he made this quite clear by reviewing the effect of excessive estrogen administration in the context of hormonal sterilization (67,68). By that time (actually in 1929) the first estrogen, estrone, had been isolated in crystalline form both by Edward E. Doisy (b.1893) at the Laboratory of Biological Chemistry, St. Louis University School of Medicine, St. Louis, (69,70) and by Adolf Butenandt (b.1903), then at the Allgemeine Chemische Universitätslaboratorium in Göttingen (71,72). Purified ovarian extracts continued to be used for some time. However, experiments were conducted with these extracts which eventually led to new concepts of a positive and a negative feedback effect of ovarian hormones upon the anterior lobe of the pituitary and its gonadotropic function. This function had been proven to exist in 1926 by Philip Edward Smith (b.1884) of the Anatomy Department at Stanford University (73,74) and by Bernard Zondek both of whom transplanted pituitary tissue into immature animals (75,76). This work was followed by the first experimental demonstration, in 1931, of a follicle stimulating and a luteinizing hormone of the anterior pituitary by Harry L Fevold (b.1902), Frederik L. Hisaw (b.1891) and Samuel L. Leonard (b.1905) (77) in the Department of Zoology at the University of Wisconsin in Madison. These investigators also contributed to elucidation of the interactions between pituitary and gonads. There is no space to tell here the story of the unravelling still going on at present of these most complex relations in females. Suffice it to say that all these studies provided a basis for the understanding that the paradoxical findings mentioned earlier (such as decrease or increase of ovarian weight in response to ovarian extracts) were caused by inhibition or stimulation of release of gonadotropins. Inhibition of gonadotropins, then, probably was the cause of sterility in some of Fellner's animals. Woldemar Reiprich (b.1899) at the Klinik of Ludwig Fraenkel (1870-1951) in Breslau suggested such a mechanism. He not only

re-emphasized Fellner's concept of different dose-dependent actions of estrogens, but also, though cautiously and only as an alternative to the concept of direct action upon the ovary, proposed that the excess estrogen might cause infertility by interfering with pituitary function (78). In 1939, ten years after the first isolation of an estrogen, reviewers spoke of the "wide acceptance of the idea that estrogens depress gonadstimulating function of the anterior pituitary... and so secondarily inhibit growth of ovarian follicles" (79). Such inhibition would of course cause sterility.

By 1939, still other actions of estrogen which could account for the infertility of treated animals had been detected. First of all, by then it had been clearly demonstrated that the effects observed by Fellner, Loeb and many others (80-88) were indeed caused by estrogens and not by other substances present in more or less purified extracts. The inhibitory effect of a pure estrogen upon the ovary was first shown in young rats. It had been known previously that ovarian extracts could retard development of ovaries in the immature animal. In 1931, Doisy and his coworkers reported that this effect could be obtained by administration of high doses of estrone (89). Progressive hydropic degeneration of the germinal epithelium and almost complete inhibition of ovulation and corpus luteum formation were found. In Doisy's laboratory, the effects of both estrone and estriol were also studied in adult rats (90). After 25 days of treatment, the ovaries of these rats showed very small follicles and very small congested corpora lutea (luteinized follicles?). In any case, the animals which had received either high doses of estriol or estrone remained infertile for some time after cessation of treatment, whereas those rats which had received low doses of estriol conceived immediately after treatment was discontinued. Fertility was not tested during the course of treatment.

In 1935, another study of the effect of estriol in rats was less conclusive (91). Simultaneously, however, Carl Clauberg (1898-1957), a gynecologist at the University of Königsberg and known for his progesterone test, demonstrated beyond doubt that estradiol (given as benzoate) completely sterilized mice while they were being treated (92). Clauberg found corpora lutea in the ovaries of the test animals. That same year, Harold Ormond Burdick (b.1897) and Gregory Pincus (1903-1967) at the Laboratory of General Physiology at Harvard University, in a classic contribution, discovered a mechanism by which mice and rabbits can be rendered infertile though they continue to ovulate (93-96). Burdick and Pincus found that moderate doses of estrone or estradiol led to retention and degeneration of blastocysts in the Fallopian tubes before they were capable of implantation and before they reached the uterus. Here, then, was an explanation

for Fellner's earlier observation which, incidentally, was not known to Burdick and Pincus. Fellner's hypothesis of the egg-damaging action of estrogens was thus shown to be correct. In a later study, Burdick and Rae Whitney (b.1914) then at the Department of Biology of Alfred University in Alfred, New York, showed that massive doses of estrone led to an accelerated passage of fertilized ova through tubes and uterus and their eventual degeneration thereby also causing infertility (97-99).

Finally, it should be mentioned that still another mechanism of the antifertility action of estrogens was described during the 1930's. Earlier observations (100) had suggested that infertility might result from a uterine factor. In 1930 Hisaw and Leonard showed that estrogen-containing extracts inhibited the action of corpus luteum extracts upon the endometrium (101). Several years later, Curt Bachman (b.1897), of the Department of Biochemistry at McGill University in Montreal, confirmed this by administering estrone and eventually observing complete inhibition of the progesterone effect upon the endometria of rabbits which continued to ovulate (102). It was later shown that such endometria would not allow implantation of the fertilized egg.

During the 1930's, then, the antifertility action of estrogens was established beyond doubt. The mechanism was shown to be either antiovulatory, antiendometrial or antifertile (involving tubal and uterine factors). Fellner's hypotheses were amply verified. Haberlandt's concept of hormonal sterilization, although extended to estrogens and to different mechanisms of action, was nonetheless generally confirmed.

CONCLUSIONS

Fellner's contributions to reproductive endocrinology were many. His pioneering work with ovarian and, in particular, with placental extracts (15,29) has been cited repeatedly as has been other work of his - not discussed here-e.g. the discovery of estrogen activity in testes (103,104) and the demonstration of an inhibitory action of estrogens upon testes (37). His contributions to hormonal sterilization, however, reported in 1922 (6) and 1927 (9,39) have been forgotten. In this regard, Fellner's major achivements were: The detection of the antifertility action of estrogen containing extracts, the hypothesis that estrogens might cause sterility by damaging the egg, and the hypothesis that estrogens act differently dependent upon their dosage. In the early 1930's when pure estrogens became available, other investigators (without being aware of Fellner's publications) showed his hypotheses to be correct. Here, as in the case of Haberlandt, is another example of important work and hypotheses not being given proper recognition, neither by contemporaries nor by successors. In the case of Fellner, one reason for this neglect may have been his mode of publication. In 1922, he only briefly announced his results in a clinical

discussion. In 1927, he reported his findings in more detail, but in general clinical journals apparently not read by investigators in the field, in particular not by those who conducted the first studies with pure estrogens. All this reminds one of the fate of the gynecologist Robert R. Frank (1875-1949) of New York, who mentioned in 1922 the uterotropic action of follicular fluid in an article written for a general medical journal (105) - as Corner has expressed it, "an unfortunate way in which to announce a potentially valuable finding" (106). It should further be mentioned that Fellner's way of reporting his findings and conclusions was somewhat disorganized and mixed with clinical observations; it failed to conform to the pattern followed in first-rate publications of that time.

Another factor was, of course, that Fellner did not work with pure hormones; the same was true of Loeb. Nonetheless, these investigators using purified extracts, achieved remarkable results. Much of what later researchers accomplished with pure hormones was at best rediscovery, confirmation or extension.

Finally, it should be noted that Fellner was a clinician who conducted basic research in reproductive endocrinology only in his spare time. The line of outstanding gynecologists who did likewise began with Knauer, Halban (17), and Fraenkel (107) who conducted their studies in an era when only a few basic scientists were interested in the endocrinology of reproduction. Fellner's contributions to this field occurred when it was better established as a new branch of science. Unlike Knauer and Halban, but like Fraenkel, Fellner continued basic experimental studies in his later years. He was the first gynecologist to confirm and support Haberlandt in his crusade for hormonal sterilization. This, of course, raises the question whether or not Fellner tried this method on his patients. As far as can be determined the answer is that he did not. We are left, then, with the question why hormonal sterilization did not conquer the human field in the late 1920's and early 1930's when both a physiologist (Haberlandt) and a gynecologist (Fellner) as well as many others were demonstrating in animals the efficiency of that method. An answer will be suggested in a subsequent paper (108).

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MEDROXYPROGESTERONE ACETATE AS AN INJECTABLE FEMALE CONTRACEPTIVE

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ABSTRACT

A total of 723 patients began receiving depo-medroxyprogesterone acetate (DMPA), 150 mg every three months, in the 21-month period from April 1967 to January 1969. This medication is a long-acting parenteral female contraceptive agent. One pregnancy occurred. Seventy-three women who subsequently had tubal ligation or hysterectomy were excluded from the analyses of continuation of DMPA. At 12 months 56.8 women per 100 and at 18 months 49 per 100 were continuing use of the medication. Irregular vaginal bleeding was the major medical reason for discontinuing use. Normal menses had not resumed within one year in 24 percent of the women discontinuing DMPA. This medication has an application in family planning practice for women who do not plan to have more children.

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