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Contraception 82 (2010) 119–124

Contraception

Editorial

Joseph W. Goldzieher and the birth of hormonal contraception

Gregory Pincus has been rightly celebrated as the "father of the Pill" for his pioneering work on the inhibition of ovulation through the administration of progestins, energizing the entire field of contraception and setting the stage for all the developments that followed (see Refs. [1–3]). This, however, should not result in a lack of acknowledgment of the many pioneers who transformed an idea into dozen of products used by tens of million of women.

One of them, Joseph W. Goldzieher, who turned 90 on 2009, is still very much intellectually and physically active. Thus, on the occasion of reaching his 10th decade, it seemed natural to me to summarize his lifetime achievements and his indefatigable efforts to improve the condition of women's health the world over.

Goldzieher was born on September 21, 1919, in Budapest into a family of famous physicians: his grandfather Wilhelm (Vilmos) was Professor of Ophthalmology at the University of Budapest and wrote numerous scientific monographs and articles; he was one of the chief contributors to Eulenburg's *Realencyclopädie der Medicinischen Wissenschaften*; in 1881, wrote *Die Therapie der Augenkrankheiten*; in 1890, published the first manual of ophthalmology written in Hungarian (*Szemèszet Kèzikönyve*). In 1903, he was decorated with the officer's cross of the Order of Franz Joseph. In addition, Wilhelm's brother, Ignác, is considered one of the founders of modern Islamic studies in Europe.

Max Goldzieher, his father, was an internationally recognized pathologist and endocrinologist and an officer in the Austro-Hungarian Army. After coming to the US, he continued his research, working for many years at St. Clare's Hospital and in private practice in New York. He was a founder of the Hungarian American Medical Association and received their highest award, the "Semmelweis Prize," giving, at age 80 a 1-h address without notes on the history of endocrinology at the New York Academy of Medicine. He is the author of many books and articles on endocrinology (e.g., Refs. [4–6]) and published several articles with his son Joseph (e.g., Ref. [7]). The family tradition in reproductive health research continues with Goldzieher's daughter, Michele Goldzieher Shedlin, a medical anthropologist and a professor at New York University.

The family traces its origin and name to 15th century Spain where they produced the gold threads utilized in filigree jewelry and to decorate or embed in the famous Toledo steel (hence, the name *tirador de oro* or *gold zieher* in German). The family moved from Hungary when he was 7 years old and settled in New York. Young Joseph went to Harvard and did medical training at New York University and at Duke University in North Carolina. Initially, he practiced medicine and did research with his father. Then, in 1952, with a daring move, he gave up a Park Avenue private practice, moved to San Antonio, Texas, to the Southwest Foundation (SWF) which was — at that time — located in a farmhouse and a hay barn (his laboratory). In retrospect, he considered this move "the smartest thing I ever did, to stay away from big institutions and try to be a visible fish in a small pond." Fortunately, the National Institutes of Health was very supportive of Goldzieher and a small, nonuniversity research establishment trying to get started. That small institution now has a net worth of $200 million and a research budget in the tens of millions. In the early days at the SWF, his friend and associate Leonard R. Axelrod convinced him to join him in buying opal rock by the kilo from Australia. When Axelrod, an expert in cutting stones, went to work, they found a treasure trove of fine opals and a new hobby for Goldzieher.

Goldzieher has been a successful clinician as much as he was a skilled scientist: he saw patients for 64 years, including endocrine consultantships for the US Army at Brooke General Hospital and for the US Air Force at Wilford Hall Hospital (in San Antonio), both for 25 years. In 1981, he began to commute weekly to Baylor College of Medicine in Houston as Professor and Director of Endocrine Research until his retirement in 1992. In 2000, the American College of Endocrinology honored him with their Lifetime Achievement Award and the title of "Distinguished Clinician," the eighth person to be so honored at that time. His acknowledgement of the award received a standing ovation. At present, he resides in San Antonio with his wife of more than 50 years, where he practiced until the age of 87, when his office building demanded a 5-year lease reinforcing his decision to retire. His last paper (to date), publication number 490, was published at age 88 [8], demonstrating his continued interest in scientific progress.

He joined the Editorial Board of *Contraception* from the first issue and continues as a member to this day.

0010-7824/$ – see front matter
doi:10.1016/j.contraception.2010.03.008

I have known "Joe" Goldzieher for over 40 years and have personally experienced his "caustic wit" and demanding commitment to excellence. He has always had little patience with what he considered flawed science, especially studies that negatively affected health care, informed patient choices and the quality of women's lives. He is well known for entering controversies head-on and, thus, has made lifelong friendships as well as permanent enmities. One episode dating back to the seventies will exemplify his typical approach to a controversial topic. I was trying to organize a conference at the World Health Organization (WHO) in Geneva and personally called Doctor Philip Sartwell, the first epidemiologist to carry out a case/control study showing an increased risk of deep vein thromboembolism in users of combined oral contraceptives (OCs) [9], to invite him to the conference. He accepted with pleasure and asked a few questions, including the names of those who would also participate. In replying, I mentioned, among others, the name Goldzieher upon which he immediately declined to join us. I reassured him that it was WHO's policy to allow each participant to freely state her/his position, but his reply was without appeal: "I do not sit in the same room with Goldzieher." I was curious and called my friend: "Joe, what did you do to Sartwell?" I asked. He candidly replied that he was present when Sartwell first presented his data on thromboembolism and the pill. To reach statistical significance in the presentation of his data, Sartwell had had to pool very different risk estimates from five US cities, with the highest risk in Baltimore and no increased risk at all in New York City. Goldzieher then publicly asked Sartwell, "If a woman in Baltimore wanted to take the pill safely, would you advise her to move to New York City?"

Goldzieher has remained an unrepentant critic of "epidemiological wisdom" all his life. As recently as 2006, in a commentary in *Contraception* [10], he blamed a "small coterie of English and American epidemiologists focused on the adverse effects of OC, with the English leading the van." In his view, "the negative impact of the reports linking thrombotic events, heart attacks and strokes to the use of combined OCs (COC), was felt for decades — as documented by surveys made in 1985 and 1994 by the American College of Obstetrics and Gynecology of the public's perception of the risks and benefits of OC use." Ten years previously, he had reviewed evidence for a causal relationship of all major adverse effects of COC concluding: "In many instances, a cause-and-effect relationship appears to be incorrect or highly improbable. In other instances, the side effects are clinically insignificant or so rare as to be of minimal importance. Yet, they continue to be listed by various authorities as validated side effects or relative contraindications to OC use. This, in turn, limits the access of many women to a highly effective form of contraception" [11]. Goldzieher also believed that "The entire matter of cardiovascular hazards related to OC use has been called into question by studies of mortality statistics in the US, Great Britain and Taiwan. In none of these studies is the predicted mortality from cardiovascular disease in OC users confirmed" [12].

At least, in part, his views have today been accepted and incorporated into the WHO list of Medical Eligibility Criteria for contraceptive use [13].

Joseph Goldzieher is a man of many scientific accomplishments, although he will be probably best remembered for his early clinical and metabolic studies on COC.

But what did he do that was different from the others in the field? The full list of his achievements will be too long and I shall simply highlight some of his scientific achievements:

He published his first paper 65 years ago [14]; at age 27, discovered that nicotinic acid given intravenously cured the severe headaches following spinal taps [15]; and in 1948, developed a new method for measuring urinary pregnanediol [16]. From the earliest days, he focused his attentions on estrogens. In 1949, with his father, he was the first to study their effects on the human skin [7] and, with Roberts, to identify estradiol in the human testis [17]. By 1960, he began a series of studies on the steroid hormones of the adrenals, ovaries and testes (e.g., Refs. [18–20]) that continued well into the 1990s.

His group became involved in oral contraception right after Gregory Pincus presented his first data at the International Congress of Endocrinology in Tokyo in 1955 [21]. At the time, the Medical Director of the Population Council was Warren Nelson and he immediately contacted Goldzieher, told him about the Council's work, asking if he would be interested in joining this new field of research. Goldzieher had already been involved with the administration of several progestins, including medroxyprogesterone acetate [Depo Provera (DMPA)] for possible applications in gynecological conditions; so for him it was a simple switch to look at contraceptive use. Together with Zañartu and Rice-Wray [22], he was the first to publish a paper on the use of Depo Provera for contraception. In 1966 they conducted a trial in Mexico and Chile in 310 subjects, including a large group of postpartum, lactating women, utilizing several different regimens. DMPA was administered as a single injection to 210 women at doses ranging from 200 to 1000 mg; all other subjects received DMPA, 150 mg, in association with a long-acting estrogen, estradiol polyphosphate (EPP), 40 mg, given every 3 months. There were three pregnancies after a single injection of DMPA alone (dosage not reported), all occurring 10 and 11 months after the injection. In this first trial, they correctly identified the most important adverse effect of long-acting progestins: "a complete disorganization of the menstrual pattern, with intermittent periods of amenorrhea, spotting, or bleeding." They also noted that: "The latter was seldom heavy." Interestingly, they did not observe any difference in bleeding patterns between women given DMPA alone compared to those administered the combination of DMPA and EPP. Possibly, this was due to the long duration of action of EPP. Finally, they observed that after DMPA 500 mg, return of menses was complete in 9 months, whereas it took 10 months in the case of 1000 mg [22].

In the 70s, Goldzieher joined the activities of the WHO Program of Research in Human Reproduction, becoming an active member of the "Task Force on Long-acting Contraceptives" and, in this capacity, was instrumental in moving forward the entire field among strong opposition. Thanks to the work of the WHO group of dedicated scientists and clinicians, another long-acting injectable agent, consisting of 200 mg of norethindrone enantate (NET-EN), was developed; large, comparative trials proved that, whereas DPMA was fully effective for 90 days, NET-EN effect began decreasing after 60 days [23,24]. Strong advocacy from the group made injectable contraception almost ubiquitously available, with the notable exception of the United States where ideological opposition delayed approval of Depo Provera as a contraceptive by the Food and Drug Administration until October 29, 1992.

Goldzieher was the second scientist in the world, after Pincus, to investigate COC. His clinical work began in 1959 in Mexico and he presented this work for the first time in 1960 in New York [25]. Interestingly, in publishing his data in the proceedings of the Conference, he named COC a "physiological method of conception control," highlighting the belief prevailing at the time, that using a progestin to block ovulation was to mimic nature. The first combination he tested contained ethinyl estradiol (EE) 60 mcg and norethindrone (NET) 10 mg [26]; but — typical of his character — he also became a strong advocate of contraception and fought all the battles with those he called the "naysayers" [27].

His group was the first to publish information on return of fertility after COC, an important issue in these days, since some investigators were convinced of the existence of a specific syndrome called "post-pill amenorrhea." Their data provided a much-needed, first-hand reassurance that women would quickly resume fertility after terminating oral contraception: 62% of a group of 42 women who discontinued therapy (even after 20 months of use) became pregnant 1 month after discontinuing medication [28]. Goldzieher concluded: "the disruption of normal pituitary–ovarian relationship by norethindrone is immediately reversible even after 2 years of cyclic treatment."

In the 60s, it was generally believed that inhibition of ovulation could only be achieved through the progestin and that the role of the estrogen was purely that of allowing a proper cycle control. Goldzieher was the first to suggest that — at least at the dose of 60 mcg — EE inhibited ovulation by itself. This intuition stemmed from the work he had done at Duke University in 1947, where he was trying to relieve patients of dysmenorrhea by inhibiting ovulation with an estrogen [29]. Of course, he had no idea of the contraceptive implications, but armed with this knowledge, he was later able to raise questions as to the role of the estrogen in COC. His group was the first to demonstrate the unique ovulation-inhibiting potency of ethinyl-estrogens as compared to other estrogens, and reported these findings at the 1964 Endocrine Society Meeting [30]. This new information was then published [31] and led to the concept of "sequential COC." In 1968, Goldzieher published two papers on the large experience accumulated with a sequential pill marketed in the USA as "C-quens." The first report [32] presented a total of approximately 149,000 cycles of experience obtained in 27 centers, in the vast majority in the United States, using 80 mcg of mestranol (MST) for 20 days and 2 mg of chlormadinone acetate for 5 days. The second reported 7 years of experience in the same centers, with some 202,000 cycles recorded. The dosage was found to be adequate for each hormone to suppress ovulation and enhance subsequent shedding of the endometrium. They reported 162 pregnancies (0.96 pregnancies per 100 women-years), with no apparent impairment of post-treatment fertility, no fetal abnormalities in subsequent pregnancies and 11 episodes of thrombophlebitis in 10 women (0.71 per 1000 women per year) [33]. Sequential regimens were later abandoned because of an increase in endometrial hyperplasia and even cancer in women using them [34].

For years, Goldzieher and his group continued to investigate the role of the estrogen component of COC. Since MST is rapidly converted to ethinyl estradiol (EE), the latter estrogen is used almost exclusively in currently marketed COCs. For this reason, they concentrated on EE and were able to prove that 19-nor progestins (such as NET) synergize with EE in inhibiting pituitary activity [35–37]. This steroid, like natural estradiol, belongs to the class of compounds that undergoes a hepatic first-pass effect and enterohepatic recirculation [38], and possibly because of this characteristic, Goldzieher was able to prove great individual variability in its pharmacokinetics, showing that, given orally, EE is very rapidly absorbed: 90% of it during the first hour in the majority of subjects. However, some individuals take as long as 2 h to fully absorb it. Peak blood levels are usually reached within an hour or two, but in some women, it may take as long as 6 h [39]. Bioavailability ranges from about 25% to 65% of the amount ingested, and elimination half-life ranges between about 6 and 27 h [40]. His work on individual variability in the absorption and disposition of EE led to an interesting conclusion, made studying the pharmacokinetic of three bioequivalent NET/MST-50 mcg and three NET/EE-35 mcg COC formulations: "The large variation in blood levels of ethinyl estradiol and norethindrone between and within individuals may overshadow clinical differences attributable to differences in dosage" [41]. In recounting the history of estrogens, Goldzieher pointed out "a fortunate accident," namely, that the early clinical preparations of synthetic progestins tested as OCs contained about 1% contamination with MST, due to the manufacturing process. While this quantity appeared trivial to the chemist, the presence of about 150 mcg of MST in the original 10-mg doses of the 19-norprogestins could have accounted totally for their contraceptive efficacy [12].

Given his general interest for contraception, it was only natural that after focusing on estrogens, Goldzieher would also become involved in studying the role of progestins in

COC and, more specifically, their effects on the endometrium. As early as 1963 [42,43], he concluded that in spite of major chemical differences between C21 and 19-nor steroids, the effects of 20-day treatments were very similar, in the sense that they all "produced early secretory changes followed by glandular involution, while stromal edema and pseudodecidual changes continued to progress. In other words, prolonged (i.e., 20-day) cyclic treatment with progestational compounds leads to early development and rapid involution of the endometrium, with only quantitative differences distinguishing the effects of one compound from another.

A field to which Goldzieher devoted attention and efforts is that of the disorder we today call polycystic ovary syndrome (PCOS) but, in the days of his work with Axelrod, was still known as the "Stein-Leventhal syndrome." They were the first to identify in vitro the enzyme defects in ovarian tissue [44] and in 1992 discussed various hypotheses on its pathogenesis and therapeutic options beyond wedge resection [45]. They noted that a number of hypotheses had been formulated; one involved elevated estrone levels that increase the sensitization of luteinizing hormone secretion and reduce that of follicle-stimulating hormone, while another implied that progesterone deficiency facilitates PCOS. He went on discussing treatment options: from night time small doses of corticosteroids for 20–30 years (favoring dexamethasone over prednisone or prednisolone), to short cycles of clomiphene citrate, to the administration of progesterone, or bromocriptine, although he admitted that studies with this compound have not shown promise. He also mentioned gonadotropin and gonadotrophin-releasing hormone as possible means of inducing ovulation in PCOS women and pointed out the beneficial effects of weight reduction. Finally, he reviewed different laparoscopic techniques to induce ovulation in these patients: sharp puncture, electric current and laser vaporization, or endocoagulation of the cysts.

Goldzieher latest battle has been fought in defense of postmenopausal women. He considers menopause (aside from its psychosocial implications) as a deficiency disorder analogous to hypothyroidism in approach and treatment [46,47].

In 2000 a study published in the *Journal of the American Medical Association* (JAMA) found that "combined hormone replacement therapy" (HRT) is associated with a higher risk of acquiring breast cancer than is estrogen-only replacement therapy (ERT) [48]. As associate editor of the "Contraception Report," Goldzieher was quick to comment that "in the *JAMA* study the 95% confidence limits of the relative risk (RR) of ERT (1.0–1.4) and combined HRT (1.1–1.8) overlap completely, indicating no important difference. Other similar studies also have confidence limits that overlap completely, subsequently demonstrating its insignificance. Hence, it is clear that the overall RR of breast cancer related to ERT or combined HRT ranges from small to nil." [49]. Two years later, Goldzieher reacted strongly to the publication of the now famous Women's Health Initiative (WHI) initial report on risks and benefits of combined hormonal replacement therapy [50] and, with his usual brutal frankness, defined it as a typical "feminist distortion of a badly designed and worse interpreted, misbegotten piece of epidemiology, rejected from the outset by a committee of experts appointed by the International Menopause Society, among others." He immediately wrote a critique in which he singled out every weak point in the study [51] and was comforted to see that, a few years later, Clarke [52] reached the conclusion that "treatment of post-menopausal women with estrogen and progestin (Prempro) does not increase the risks of cardiovascular disease, invasive breast, cancer, stroke or venous thromboembolism." When McDonough wrote a comment in *Fertility and Sterility* [53] pointing out that, even double-blind, randomized-controlled studies are not without imperfections, he immediately wrote to the Editor welcoming the Editorial as an appropriate "counterpoint to the slavish acceptance of the Women's Health Initiative report by medical organizations, physicians and, of course, the media." He pointed out the "vast body of biological data—objective, reproducible, accurate experimental data—showing a multitude of beneficial effects of estrogen against atherogenesis at the organ, functional, tissue, cellular and molecular levels." He concluded: "the burden of proof is on the WHI study to show why it is not in accord with this other data, not the other way around" [54]. This letter prompted an Editorial comment by McDonough [55], who pointed out that: "Dr. Goldzieher's position as an observer and player during those 'heroic years' gives particular value to his comments. He was one of the key figures in the development of sequential contraceptive regimes and synthetic progestins. He was one of the first to point out the synergism between estrogen and progestin in ovulation inhibition and was instrumental in proposing lower-dose OCs [12]. Dr. Goldzieher knew how to spot an important discovery and always seemed to know how to navigate through the flotsam and jetsam of scientific changes to provide strong, clear statements on important scientific issue."

Today, Joseph W Goldzieher continues to enjoy his 10th decade with a fine wine, growing his orchids and maintaining a keen interest in scientific advancement, which he follows, thanks to the wonders of the Web.

Let me finish this brief overview by following the advice of Paul G. McDonough and inviting the reader to go to the web (MedLine, PubMed, Scopus, etc.) "to retrieve the most important years of Reproductive Endocrinology." He believes that from this search "you will be dismayed to realize how precious and perishable fundamental scientific knowledge can be, but you will be rewarded to learn that studies of the past can provide important scientific information for the future" [55].

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References

[1] Goldzieher JW, Rudel HW. How the oral contraceptives came to be developed. J Am Med Ass 1974;230:421–5.
[2] Diczfalusy E. Gregory Pincus and steroidal contraception: a new departure in the history of mankind. J Steroid Biochem 1979;11:3–11.
[3] Rice-Wray E. Twenty years of oral contraception. IPPF Med Bull 1981;15:1–3.
[4] Goldzieher MA. The endocrine glands. New York: Appleton-Century; 1939.
[5] Goldzieher MA. The adrenal gland in health and disease. Philadelphia: Davis; 1948.
[6] Goldzieher MA. Treatment of excessive growth in the adolescent female. J Clin Endocrinol Metab 1956;16:249–52.
[7] Goldzieher MA, Goldzieher JW. Toxic effects of percutaneously absorbed steroids. JAMA 1949;140:1156.
[8] Goldzieher JW, Stanczyk FZ. Oral contraceptives and individual variability of circulating levels of ethinyl estradiol and progestins. Contraception 2008;78:4–9.
[9] Sartwell PE, Masi AT, Arthes FG, et al. Thromboembolism and oral contraceptives: an epidemiologic case/control study. Am J Epidemiol 1969;90:365–80.
[10] Goldzieher JW. Bust without boom. Contraception 2000;61:27–8.
[11] Goldzieher JW, Zamah NM. Oral contraceptive side effects: where's the beef? Contraception 1995;52:327–35.
[12] Goldzieher JW. Estrogens in oral contraceptives: historical perspectives. Johns Hopkins Med J 1982;150:165–9.
[13] World Health Organization. Improving access to quality care in family planning: medical eligibility criteria for contraceptive use. Geneva: WHO; 2004.
[14] Goldzieher MA, Reimer NA, Goldzieher JW. Metabolic abnormalities in obesity: a statistical survey. Am J Dig Dis 1945;12:387–94.
[15] Goldzieher JW, Popkin GL. Treatment of headache with intravenous sodium nicotinate. JAMA 1946;131:103–5.
[16] Goldzieher JW. A new colorimetric method for the determination of pregnanediol. J Lab Clin Med 1948;33:251–3.
[17] Goldzieher JW, Roberts IS. Identification of estrogen in the human testis. J Clin Endocrinol Metab 1952;12:143–50.
[18] Axelrod LR, Rao PN, Goldzieher JW. Methylation of 2-hydroxyestradiol-17β to 2-methoxyestrone in the human. Arch Biochem Biophys 1960;87:152–3.
[19] Axelrod LR, Goldzieher JW. The metabolism of 17α-hydroxyprogesterone and its relation to congenital adrenal hyperplasia. J Clin Endrocrinol Metab 1960;20:283–97.
[20] Savard K, Goldweber M, Goldzieher JW. Non utilization of mevalonic acid in steroidogenesis by testis tissue. Fed Proc 1960;19:196.
[21] Pincus G. Some effects of progesterone and related compounds upon reproduction and early development in mammals. Proc. 5th Internat Conf Planned Parenthood, Tokyo. Acta Endocrin (Khb) 1956;20 (Suppl 28):175–84.
[22] Zañartu J, Rice-Wray E, Goldzieher JW. Fertility control with long-acting injectable steroids: a preliminary report. Obstet Gynecol 1966; 28:513–5.
[23] World Health Organization. Task force on long-acting injectable contraceptives. Multinational comparative clinical trial of long-acting injectable contraceptives: norethisterone enantathe given in two dosage regimens and depot-medroxyprogesterone acetate. A preliminary report. Contraception 1982;25:1–11.
[24] World Health Organization. Task force on long-acting injectable contraceptives. Multinational comparative clinical trial of long-acting injectable contraceptives: norethisterone enantathe given in two dosage regimens and depot-medroxyprogesterone acetate. Final report. Contraception 1983;28:1–20.
[25] Goldzieher JW, Moses LE, Ellis LT. A field trial with a physiological method of conception control. In: Kiser CV, editor. Conference on Research in Family Planning, New York, 1960. Princeton (NJ): Princeton University Press; 1962. p. 351–6.
[26] Goldzieher JW, Moses LE, Ellis LT. Study of norethindrone in contraception. JAMA 1962;180:359–61.
[27] Goldzieher JW. Clinical evaluation of contraceptives: a great responsibility. Yearbook Gynecol 1965-1966:371–4.
[28] Goldzieher JW, Rice-Wray E, Schulz-Contreras M, Aranda-Rossel A. Fertility following termination of contraception with norethindrone. Endometrial morphology and conception rate. Am J Obstet Gynecol 1962;84:1474–7.
[29] Haus W, Goldzieher JW, Hamblen EC. Dysmenorrhea and ovulation. Correlation of the effect of estrogen therapy on pain, the endometrium and the basal body temperature. Am J Obstet Gynecol 1947;54:820–8.
[30] Martinez-Manatou J, Gual C, Goldzieher JW, Rudel HW. Comparative antiovulatory potency of certain natural and synthetic estrogens. Program Endocrine Soc, 46th Meeting San Francisco. Chevy Chase (MD): The Endocrine Society; 1964. p. 68. [no. 91].
[31] Gual C, Becerra C, Rice-Wray E, Goldzieher JW. Inhibition of ovulation by estrogens. Am J Obstet Gynecol 1967;122:625–36.
[32] Hines DC, Goldzieher JW. Large-scale study of an oral contraceptive. Fertil Steril 1968;19:841–66.
[33] Goldzieher JW, Maas JM, Hines DC. Seven years of clinical experience with a sequential oral contraceptive. Int J Fertil 1968;13: 399–404.
[34] Kelley HW, Miles PA, Buster J, Scragg WH. Adenocarcinoma of the endometrium in women taking sequential oral contraceptives. Obstet Gynecol 1976;47:200–2.
[35] Goldzieher JW, Maqueo M, Chenault CB, Woutersz TB. Comparative studies of the ethynyl estrogens used in oral contraceptives. I. Endometrial response. Am J Obstet Gynecol 1975;122:615–8.
[36] Goldzieher JW, de la Peña A, Chenault CB, Woutersz TB. Comparative studies of the ethynyl estrogens used in oral contraceptives. II. Antiovulatory potency. Am J Obstet Gynecol 1975;122: 619–24.
[37] Goldzieher JW, de la Peña A, Chenault CB, Cervantes A. Comparative studies of the ethynyl estrogens used in oral contraceptives. III. Effect on plasma gonadotropins. Am J Obstet Gynecol 1975;122:625–36.
[38] Goldzieher JW, Brody SA. Pharmacokinetics of ethinyl estradiol and mestranol. Am J Obstet Gynecol 1990;163:2114–9.
[39] Goldzieher JW. Pharmacology of contraceptive steroids: a brief review. Am J Obstet Gynecol 1989;160:1260–4.
[40] Goldzieher JW. Pharmacokinetics and metabolism of ethinyl estrogens. In: Goldzieher JW, Fotherby K, editors. Pharmacology of the contraceptive steroids. New York: Raven Press Ltd; 1994. p. 127–52.
[41] Brody SA, Turkes A, Goldzieher JW. Pharmacokinetics of three bioequivalent norethindrone/mestranol-50 micrograms and three norethindrone/ethinyl estradiol-35 micrograms OC formulations: are "low-dose" pills really lower? Contraception 1989;40:269–84.
[42] Maqueo M, Perez-Vega E, Goldzieher JW, Martinez-Manautou J, Rudel HW. Comparison of the endometrial activity of 3 synthetic progestins used in fertility control. Am J Obstet Gynecol 1963;85: 427–32.
[43] Rice-Wray E, Aranda-Rossell A, Maqueo M, Goldzieher JW. Comparison of the long-term endometrial effects of synthetic progestins used in fertility control. Am J Obstet Gynecol 1963;87: 429–33.
[44] Axelrod L, Goldzieher JW. Enzymic inadequacies of human polycystic ovaries. Arch Biochem Biophys 1961;95:547–8.
[45] Goldzieher JW, Young RL. Selected aspects of polycystic ovarian disease. Endocrinol Metab Clin North Am 1992;21: 141–71.
[46] Goldzieher JW. Menopause — a deficiency disease. In: Rock JR, Faro S, Gant NF, Horowitz IR, Murphy AA, editors. Advances in Obstet Gynecol. St. Louis: Mosby; 1994. p. 159–78.
[47] Goldzieher JW. Menopause: a major challenge for endocrinologists. Endocr Pract 1996;2:339–41.

[48] Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 2000;284:691–2.
[49] Goldzieher JW. Media scan. Hormone replacement therapy and breast cancer risk. (Commentary) Contracept Rep 2000;11:12–4.
[50] Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
[51] Goodman N, Goldzieher JW, Ayala C. Critique of the report from the Writing Group of the WHI. Menopausal Med 2003;10:1–4.
[52] Clark JH. A critique of Women's Health Initiative studies (2002–2006). Nucl Recept Signal 2006;4:e023.
[53] McDonough PG. The randomized world is not without its imperfections: reflections on the Women's Health Initiative study. Fertil Steril 2002;78:951–6.
[54] Goldzieher JW. Heroic years. Letter to the editor. Fertil Steril 2003; 79:1258.
[55] McDonough PG. Commentary. Fertil Steril 2003;79:1258–9.