ELSEVIER

Social Science & Medicine 60 (2005) 2609–2622

SOCIAL SCIENCE & MEDICINE

www.elsevier.com/locate/socscimed

French hormones: progestins and therapeutic variation in France

Ilana Löwy[a], George Weisz[b,*]

[a]CERMES (CNRS, EHESS, INSERM), 7 rue Guy Môquet 94801 VILLEJUIF

[b]Department of Social Studies of Medicine, McGill University, 3647 Peel Street, Montreal, Que. Canada H3A 1X1

Available online 19 December 2004

Abstract

Western medicine is seen as universally valid, but in reality it displays a wide range of national and local variability. Our paper focuses on one such case of local variation: the widespread use of progestins in France to treat various pre-menopausal conditions as well as for contraception. The case of progestins allows us to explore how specific styles of research may come to dominate a particular local medical culture, and how they are influenced by changing criteria of scientific validity and wider social relations. We argue that in the 1980s and 1990s a single prestigious research-oriented Parisian hospital service played a dominant role in the transformation of progestins into scientifically validated medical practice. This status was not called seriously into question until recently when foreign research on a different form of hormone therapy suggested that risk was associated with their use. We also propose that both the research around and medical use of progestins in France was shaped by the positive attitude of many French women, including feminists, to hormonal therapies and to the non-surgical specialty most closely associated with hormones, medical gynaecology.

Keywords: France; Progestins; Gynaecology; Hormonal therapy; Endocrinology; Women's health

Introduction

In her book *Medicine and culture*, Lynn Payer, a North-American medical journalist working in Europe, described major cultural differences in the medical practices of several Western countries. Payer (1988, p. 21) attributed these differences in medical practices to different cultural and intellectual traditions that shape a "national character"—that is, "a conglomeration of values, priorities and actions that change over time, albeit slowly".

Cultural traditions may provide a useful explanatory framework for historical and sociological analysis. But variation in medical practice is ubiquitous even within national cultural contexts. This is now seen as a "problem" that has spawned an entire "evidence-based medicine" industry of consensus conferences, meta-analyses, and practice guidelines. There is however an alternative way to understand variation that does not focus on large cultural differences and that does not presume that it is a sign of error: in this approach one seeks to understand how a particular set of medical practices is validated, stabilized and diffused. Following a single case makes clear that the "culture" refers not only to putative national character, traditions and beliefs, but also to the more restricted cultures and practices of specific research laboratories, specialist groups, hospital wards, patient groups and economic interests. In these local settings, specific therapeutic practices and styles of research may come to predominate. Such practices and styles,

*Corresponding author.

E-mail address: george.weisz@mcgill.ca (G. Weisz).

0277-9536/$ - see front matter
doi:10.1016/j.socscimed.2004.10.021

however, are influenced by changing criteria of scientific validity.

In the following essay, we will explore one such case: the therapeutic use of progestins in France for pre-menopausal women. Despite the fact that reliable statistics are difficult to collect, it seems clear that French utilization of a wide variety of progestins has been taking place on a uniquely large scale. Our purpose is not to contrast curious or erroneous French medical practices with the supposedly more "rational" or "evidence-based" practices of British and North American doctors. British and American doctors prescribed hormones to millions of women with little in the way of support from controlled clinical trials; the key point is they did so in a way that was *different* from French practices. Our goal is thus to utilize the French case to explore some of the mechanisms for what we believe is a ubiquitous feature of all Western medicine: local variation.

Several elements enter into our analysis. The most obvious concerns the kind of problem being treated. The conditions associated with maladies related to the female reproductive system are extremely complex, fluid and multiform; they may include maladies whose somatic character no one disputes—uterine growths, dysmenorrhoea, menorrhagia—but may also include diffuse problems including insomnia, mood swings and anxiety. Such conditions may well be especially (though not uniquely) prone to disagreement and variation. A second factor is the complexity of hormonal activity. The more scientists learn about sex hormones, the more they are aware of their exceptionally complex effects, differential influence on tissues, and unstable, changing composition. This too promotes variation. A third factor that is peculiar to France is the degree of centralization that characterizes national examinations and academic competitions. Historians have long understood that, in France, the views of an influential scientist who controls examinations and academic jobs can have a significant impact on the diffusion of theories and methods.

This essay however lays particular emphasis on two other factors. The first has to do with the larger community. It is impossible in a field like reproductive endocrinology for researchers not to be influenced to some extent by service users, in this instance women, and especially the more organized and vocal elements among them. Relationships between feminist groups and doctors in France, we suggest, differed in important ways from those in the US and produced a very different climate for the development of hormone research and therapy. The second has to do with research underlying practices. Studies of variation often frame the problem in terms of inadequate knowledge of the medical literature. We in contrast assume that doctors are often quite aware of the literature but that this literature may be inconclusive and/or highly varied. Furthermore, variations in research results may be related to different styles of research.[1] In the case of gynaecological endocrinology in France, the dominant research style has involved a form of physiological, histological, and clinical investigation that has been influential everywhere in the 20th century. It is a research style that has been challenged by rival epidemiological styles of medical research that have become consolidated during the past decade as "evidence-based medicine". Although hardly unchallenged, the primacy of the prospective, double-blinded, randomized clinical trial has placed all other evidentiary systems on the defensive, even in France where it occurred belatedly (Berlivet, 2000). The history of progestins in France reflects these changing scientific norms.

The use of progestins to treat a wide range of "female disorders" is not exclusively Gallic. It is part of the larger international story of hormone therapy that we will discuss in our conclusions. An even closer parallel is the widespread use in Britain of progesterone for pre-menstrual syndrome due mainly to the popular books of Dr. Katharina Dalton (1984). A variety of studies have documented this use, which has recently declined due partly to fewer diagnosed cases of PMS and partly to the increased popularity of SSRIs (Wyatt, Dimmock, Jones, Obhrai, & O'Brien, 2001; Wyatt, Dimmock, Frischer, Jones, & O'Brien, 2002).

Although some French uses of progestins (for breast pain, for instance) cover conditions similar to those classified by the British as PMS, French practices differ in several ways. The French use a wider variety of products for a wider selection of conditions and their commitment to progestins has been seen as cutting edge science. It was, we shall see, popularized not by a maverick individual physician publishing popular books but by the leading French group of reproductive endocrinologists and gynaecologists. Furthermore, the scale of the practice in France is remarkable. Considerable anecdotal evidence—including the perceptions of many French gynaecologists—and an accumulating body of quantitative data suggest that French doctors prescribe and French women purchase (these are prescription drugs) large quantities of progesterone derivatives for a variety of pre-menopausal conditions, as well as for contraception.[2] These data are particularly

[1] Many terms have been created to theorize such research styles including "paradigm", "thought style", and "laboratory cultures", but we have used a common-sense term whose purpose is essentially descriptive.

[2] Regine Sitruk-Ware has obtained quantitative data from the pharmaceutical industry indicating that in the 1980s, the consumption of progestins in France was tenfold or more than in other European countries or in the US. Interviews with R. Sitruk-Ware and G. Plu-Bureau. H. Rochefort and C. Sureau

surprising in view of the fact that French doctors on the whole prescribe sex hormones less frequently than their North American colleagues (Ringa et al., 2004).

Unpublished studies by epidemiologists Virginie Ringa and Monique Lê found that approximately one-quarter of premenopausal women in their (unselected) cohorts used a drug from this family.[3] Very preliminary results from a study carried out by Beatrice Jacqueme indicate that in the Bouches du Rhône, the health insurance system processed during the single month of April 2003 over 16,000 cases of doctor-prescribed progestogen purchases;[4] this in a population (in 1999) of 646,000 women between the age of 20 and 74. A list of the 50 most purchased drugs in France, includes two progestins, Duphaston (listed number 32 only a little behind Prozac at 29) and Lutenyl (listed 45) (Agence française de sécurité sanitaire des produits de santé, 2002). The recent Million Women Study published in *The Lancet* found a huge jump in use of HRT in the UK after menopause (Million Women Study Collaborators, 2003, p. 420). Jacqueme's Bouches du Rhône data, in contrast, shows no such dramatic contrast; almost as many women aged 40–49 take progestogens as do women aged 50–59.[5] Yet other data about post-menopausal women find that progestins are associated with estrogen replacement from three to four times more frequently than is the case in the UK, and about three times more frequently than in the US (Rochefort & Sureau, 2003).

For all these reasons it is worth looking closely at how such practices developed in France. We do not attempt to trace actual diffusion but rather ask: how does a medical practice become a scientifically validated "innovation" that can then be accepted by well-informed physicians as the "best" available therapy for patients? In answer to this question, we argue that a single prestigious and research-oriented hospital service, situated at the Necker Hospital in Paris and directed by the pre-eminent French reproductive endocrinologist of the 1980s and 90s played a dominant role in the transformation of progestins into scientifically validated medical practice; we also argue that this process was influenced by the attitudes of French women to hormones and to their gynaecologists.

From medical gynecology to sex endocrinology

In Europe and North America, gynaecology was not originally associated exclusively with obstetrics. From the 1860s on, as medical specialists proliferated, gynaecology developed as a distinct field, one of the largest of the new specialty groups that formed.[6] The dominant tendency almost everywhere in the second half of the 19th century was to claim for gynaecology an autonomous status based on innovative surgical procedures. However, by the late 19th century, pressure to unify gynaecology with obstetrics intensified for several reasons.

First, since women's diseases were defined primarily by the female reproductive system, it made little sense for many to separate this reproductive system before and after childbirth from childbirth itself. Second, given political concerns everywhere about falling birth rates and high infant mortality, the whole point of gynaecological care in young women was to ensure healthy reproduction (Moscucci, 1990). Finally, national medical associations, grappling with ways of regulating specialties, wanted to keep the number of specialties manageably small. One way to do so was to unite specialties with visible links. Thus diseases of the ear were combined with those of the throat and nose, and in some countries, psychiatry was united with neurology.

In Germany, Britain, and the US these pressures led to the unification of gynaecology with obstetrics. All the above pressures operated in France; in the discussions over specialist certification that took place during the 1930s in France, obstetrics and gynaecology were consistently treated as a single specialty. However, things turned out rather differently. The most significant reason was the historical separation of obstetrics from surgical gynaecology in Paris hospitals. During the 1870s, the hospital administration created an autonomous corps of obstetricians to carry out hospital births. Hospital surgeons agreed only on condition that gynaecological surgery was rigorously excluded from obstetrical wards, which characteristically lacked operating theatres (Bar, 1911; Lefaucher, 1988). As this separation spread to other French cities, elite gynaecology developed a professional identity distinct from that of elite obstetrics. At first this identity was largely surgical, but in the early years of the 20th century a distinctly medical orientation began to spread as well. This combination was consecrated by the creation in 1931 of the French Society of Gynecology. In addition to traditional medical therapies like electricity, massage

(*footnote continued*)
(2003, on the website of the Académie Nationale de Médecine) write that "the frequency of utilization and the great variety of progestogens is a French particularity." They cite a forthcoming epidemiological study by Francoise Clavel-Chapelon.

[3]Papers presented at a "Witness Workshop" on progestogens held June 10, 2003, at CERMES in Paris.

[4]Mme Jacqueme sent us this data on behalf of the ERSM-sudest, CNAMTS, whose local director is Charles Chamut.

[5]According to our calculations based on Jacqueme's raw data, 6% of the female population aged 40–49 took progestins with or without estrogen in April 2003; the figure for women 50 to 59 was 6.7%.

[6]This section is based on Weisz (forthcoming).

and mineral waters, practitioners utilized newer procedures like radiation, roentgentherapy, infra-red and ultra-violet rays. Starting in the 1930s, sulphanimides and hormones joined the panoply of medical procedures that could be practiced by gynaecologists. From 1934, the journal of the Society of Gynecology published alongside articles about the usual surgical procedures and methods of physical medicine, articles about various hormonal products—notably folliculine and testosterone. In the volume for 1939, seven articles (out of 32 in all) were devoted to hormones.[7] Derived from sophisticated laboratory procedures, hormonal products probably constituted the most "scientific" of the procedures available to gynaecologists who did not want to practice surgery exclusively.

When regulation and certification of specialists was introduced in France after World War II, political pressures came heavily to bear. As a result, the original plan for a single specialty in obstetrics–gynaecology was modified. In the course of negotiations during the late 1940s four distinct groups were established and these were consecrated by an administrative decree in 1949 (Weisz, 2002). The combination of obstetrics and gynaecology (OBGYN) was recognized as a full specialty that had to be practiced exclusively. Three other categories were defined as *compétences* that could be practiced either as exclusive specialties or in combination with general practice. These were surgical gynaecology, obstetrics, and medical gynaecology. Despite administrative distinctions, all four came to be seen as specialties although OBGYN was clearly the highest status option.

As a result of this realignment, the Society of Gynecology became increasingly identified with "medical" gynaecology. Articles on surgery became less frequent. Professional rhetoric emphasized the increasing separation of the field from "mutilating" surgery; the ideal became the "conservation" of reproductive organs (Marcel, 1948). Hysterectomy began to be referred to as "castration", a treatment of last resort (Sappey, 1946). Some gynaecological surgeons expressed similar sentiments (Payer, 1947; Serafino, 1946). Medical gynaecology became viewed as "an essentially conservative" specialty distinct from gynaecological surgery (Marcel, 1948). Endocrinology was at the centre of this new medical identity, and gynaecologists experimented with hormones in treating a wide variety of conditions (Ulrich, 1948, 1949; Debuc, 1949; Béclère, 1951, 1954; Rautureau & Mardrus, 1950).

By 1957, about 14,000 specialists had been certified. This figure included 647 gynaecologists, 524 obstetricians and only 416 individuals combining the two fields (Daurand, 1958, p. 3102). Despite such numbers, professional power lay with obstetrician–gynaecologists whose field was recognized as a full specialty, who had developed a strongly surgical orientation, and who dominated hospitals and medical schools. These exerted considerable pressure to eliminate medical gynaecology which they viewed as part of their natural domain. They achieved partial success as a result of the reforms of specialty training in 1982 that led to the elimination of postgraduate training in medical gynaecology (Weisz, forthcoming).

Despite its marginal status, medical gynaecology grew, becoming an increasingly feminine specialty while OBGYN remained predominantly male.[8] The political battle to legalize and make widely available contraception during the 1960s and 70s, as well as the battle to legalize abortion seems to have further alienated women from obstetrician–gynaecologists whose national representatives were perceived, correctly or not, as massively opposed to liberalization of birth control. Medical gynaecologists, on the other hand were closely associated with the forces in favour of legalization (Chauveau, 2003).

From the 1950s through the 1980s, medical gynaecologists actively studied the clinical effects of sex hormones. Pharmaceutical companies made their products available to gynaecologists in private practice who frequently published the results of their experience (Bernard, 1960; Hainaux, 1965; Rozenbaum, 1982). At the same time, several more organized research teams operating in hospitals also began researching and publishing on the subject. By far the most important was the Service de Physiopathologie de la Reproduction at the Necker Hospital in Paris headed by Arnold Netter (b. 1910), the best-known medical gynaecologist of the era.

Netter was trained as gynaecologist and endocrinologist, and went on to specialize in studies of ovarian functions and hormonal therapies of gynaecological pathologies. His main research interest was the therapy of menstrual disorders and the treatment of sterility. Netter was an active member of French Society of Medical Gynecology and published very frequently in its journal. When the Debré reform of 1958 forced hospital clinicians to choose whether to become recognized as full-time professors in the new hospital medical schools or continuing in private practice (while retaining hospital posts), Netter opted for private practice. His department developed close links with medical gynaecologists in private practice who actively participated in clinical experimentation with new hormonal therapies. He organized highly popular conferences presenting new

[7] See the *Comptes Rendus de la Société française de Gynécologie*, *9* (1939).

[8] In 1984, almost 70% of medical gynecologists were women making it the most feminine specialty; among obstetricians the figure was less than 10%. See the Conseil National de l'Ordre des Médecins (1985).

developments in gynaecology and endocrinology to medical practitioners and published an important textbook in 1949 and last updated in 1969.

Mauvais-Jarvis' School

Netter retired in 1975. His successor, Pierre Mauvais-Jarvis (b. 1929) changed the department's name to "Endocrinology and Reproductive Medicine" taking it well beyond the sphere of traditional gynaecology. Mauvais-Jarvis had been trained as a clinical endocrinologist and was recruited in 1963 as researcher in the CNRS (the French National Research Centre); but he decided to combine laboratory research with hospital practice. He became professor of endocrinology at Pitié-Salpétriere Hospital (in 1966)—and was elected vice president of the French Society of Endocrinology in 1967, before moving to Necker. Mauvais-Jarvis did not become a member of the French Society of Gynecology until 1982. He maintained more distant relationships with the gynaecologists who collaborated with his department and, unlike his predecessor, obtained a university professorship in reproductive endocrinology along with the direction of the Necker service, thanks to the support of the Minister of Health, Simone Veil. In 1975, the French parliament voted—after stormy debates—the "Veil Law", which legalized abortion; a law the previous year made contraception, legalized in 1967, more widely available. Veil thus wished to promote research in reproductive endocrinology. The early identification of the Necker service with what amounted to women's rights issues would profoundly mark its activity.

The holder of the sole chair of reproductive endocrinology in the country, and the author of a major gynaecology textbook, Mauvais-Jarvis became widely recognized as the leading expert in this field. He became engaged with practical issues of gynaecology through his pioneering work on percutaneous administration of sex hormones. In the late 1960s he developed a close collaboration with a small pharmaceutical company, Besins-Iscovesco (with which he had family links) and helped them to develop percutaneous preparations of estrogens that became highly popular in France. Mauvais-Jarvis also developed percutaneous preparations of progestins and searched for clinical applications. At this time, the Necker school, like French gynaecologists generally, sought to provide individually tailored hormonal therapies by tinkering with doses, administration pathways and molecules. In this respect, they did not differ substantially from doctors in other countries.

Mauvais-Jarvis, however, disagreed profoundly with some American researchers about appropriate ways to evaluate risks of medications. In the US, scientists frequently tested drugs on laboratory animals. Unfortunately (according to the French), the "standard laboratory animal" they used in hormone research, the beagle dog, happened to be especially sensitive to carcinogenic effects of progestins, and easily developed breast tumours; consequently the Americans dismissed Luteran, a progestin widely used in France with no apparent ill effects. In contrast, French endocrinologists preferred to observe physiologically women who used hormones; the most convincing level of proof involved biopsies and analysis of substances in the blood, coupled with self-reported observations of the drug's users. Research pursued by Netter's and then Mauvais-Jarvis's group relied on observational data (temperature curves, analysis of cervical glare) and measurement of hormone levels in the urine and in the blood. One of the goals was to correlate biochemical with clinical observations and with histological analyses of breast and endometrial biopsies. The latter technique cannot be used very often because the procedures are painful and may be traumatic to patients, but data provided by biopsies were considered especially reliable when done by a skilled cytologist. The Necker group's cytologist, Mme Yaneva, had a reputation for almost supernatural skills; she was credited by her ex-collaborators with an ability to identify the type of progestin used by a woman solely through examination of an endometrium biopsy sample (Netter, 1981b).

Studies of progestins undertaken at the Necker Hospital reflected this dominant physiopathological research style. From the mid-1960s on, the marketing of progestins that could be taken *per os* and that did not induce androgenizing effects allowed these molecules to be tested in the treatment of a wider range of gynaecological disorders, including uterine fibroids, endometriosis and benign breast disease.

The luteal insufficiency hypothesis

One of the topics investigated by Mauvais-Jarvis was the treatment of breast pain. "Mastodynia" is a frequent feminine complaint, linked to several conditions: premenstrual syndrome (PMS), cystic mastitis, polycystic disease of the breast, fibroadenomas, and perimenopause (Mauvais–Jarvis & Kuttenn, 1974). Breast pain had certainly been discussed in North American and European medical literature since the 1940s, and a variety of therapies had been suggested, including non-steroid pomades, vasculotropic substances, antiprolactinic drugs, or tranquilizers (Love, Gelman, & Sleen, 1982). Katherina Dalton championed from the 1950s the use of natural progesterone to treat breast pain linked with PMS (Dalton, 1959, 1984; Green & Dalton, 1953). Similar recommendations were made by Belgian and French gynaecologists (Vokaer, 1954; Ruf, Coddacione, & Gernent, 1964). However, until the 1980s, benign

breast disease received relatively little medical attention in France and other nations because it was perceived as a relatively minor complaint (Lambert & Netter, 1956; Netter, 1960). Mauvais-Jarvis and his students transformed it into a major subject of endocrinological investigation receiving extensive attention from French researchers.

Mauvais-Jarvis subscribed to the view that cyclic breast pain is hormone-dependent, induced by minor and temporary lowered levels of progesterone; this justified progestin therapy (Mauvais-Jarvis, Kuttenn, & Ohlgiesser, 1974; Mauvais-Jarvis, Kuttenn, & Wright, 1975; Mauvais-Jarvis, Sitruk-Ware, Sterkers, & Moszowicz, 1977a). Mauvais-Jarvis initially viewed such treatment of benign breast disease as a way to alleviate the physical and psychological suffering of women (Mauvais-Jarvis, 1972). Two year later he proposed another rationale: that benign mammary disease is a significant risk factor for breast cancer (Mauvais-Jarvis & Kuttenn, 1974). Drawing a parallel with the view that unopposed estrogen can induce endometrial cancer, Mauvais-Jarvis proposed that a disturbance of the estrogen/progesterone equilibrium may also lead to an excessive proliferation of breast tissue. Epidemiological studies, he argued, confirmed this link. Benign breast disease was not a "pre-cancerous state" but rather a "marker" for the existence of a hormonal disequilibrium and breast vulnerability. This added a further justification for progestin therapy to redress such disequilibrium (Mauvais-Jarvis & Kuttenn, 1975).

The Necker group elaborated and extended the "luteal insufficiency" hypothesis in a series of articles published between 1975 and 1980 (Mauvais-Jarvis, 1975; Mauvais-Jarvis & Kuttenn, 1975; Mauvais-Jarvis & de Lignières, 1976; Mauvais-Jarvis et al., 1977a; Mauvais-Jarvis, 1978a; Mauvais-Jarvis, Sitruk-Ware, Kuttenn, & Sterkers, 1979; Mauvais-Jarvis, 1979a; Kuttenn, Martin, & Mauvais-Jarvis, 1979). The arguments in favour of this hypothesis were grounded in histological observations, biochemical studies, and indirect epidemiological considerations. The Necker group developed two parallel claims: (1) luteal insufficiency is the underlying cause of benign mastopathies and (2) it may also play a role in the genesis of breast cancer. The first claim was grounded in physiological data (measures of levels of circulating hormones, temperature curves, cytological observations) and was presented as a clinical fact. The second, by contrast, was presented as a hypothesis, grounded in a hypothesized parallel between the "fibrocystic disease" of the uterus known to be induced by estrogen/progesterone imbalance and proliferative changes of the breast (Sitruk-Ware & Mauvais-Jarvis, 1983). Although Mauvais-Jarvis retreated from his initial proposal for generalized preventive progestin therapy (Mauvais-Jarvis & Kuttenn, 1975), he continued to advocate its use in all symptomatic cases (Mauvais-Jarvis, 1978a).

To sum up, the luteal insufficiency hypothesis emerged from a pathophysiological style of research that had been well established in France for over a century. Physiological research led to a notion or hypothesis about the mechanism behind a disease process or condition. A therapy was conceived to deal with this underlying mechanism. Once patients responded symptomatically, further research was conducted to trace the physiological changes behind the apparent improvement by measuring various functions. In this particular instance, Mauvais-Jarvis began with the hypothesis of luteal insufficiency as a source of many pre-menopausal symptoms particularly those involving the breast. The logical therapy was to provide progestins of various types and in various combinations to see which worked best symptomatically. Simultaneously, chemical assays of the blood and urine, temperature curves, and histological analysis of tissue from biopsies in order to determine hormonal levels and endometrial changes sought to illuminate the inner workings behind the symptomatic improvement. Once he became convinced that progestins could protect against breast cancer, he and his collaborators attempted to elucidate the mechanisms responsible for that effect. Explaining the biochemical mechanism responsible for progestins' putative anti-proliferative action on breast cells would be considered a quasi-definitive proof within this research style.

Defending the luteal insufficiency hypothesis

In 1974, Sherman and Korenman published the influential "estrogen window hypothesis" that linked the genesis of breast cancer to a relatively short periods in women's reproductive life during which she may be exposed to an excess of estrogen induced by a luteal insufficiency (Sherman & Korenman, 1974a,b). Mauvais-Jarvis enthusiastically endorsed this hypothesis (Mauvais-Jarvis & Kuttenn, 1975, p. 326). However researchers in the US and UK who aspired to neutralize the (putative) harmful effects of the "estrogen window" turned not to progestins but to non-steroid anti-estrogens, like tamoxifen (Pike, Krailo, Henderson, Casagrande, & Hoel, 1983). The biochemistry-oriented Necker group attempted to mobilize support for their views through research focusing on physiological and cellular mechanisms that suggested progestins promote a maturation of breast cells and/or inhibit their proliferation (Mauvais-Jarvis, 1985b).

Physiological and biochemical studies of benign breast disease provided a model for studying the relationships between hormones, hormone receptors, and uncontrolled proliferation of breast cells. They also

linked the two major domains of activity of the Necker group: fundamental endocrinological research and cure of common gynaecological disorders. At first the group studied the effects of progestins on breast cells in women who underwent breast biopsies. Occasionally patients who were to undergo surgical procedures such as breast reduction were asked to apply a hormone preparation to the breast before the operation in order to study its effects on breast cells. The aim was to correlate morphological and histological changes in breast tissue with data on hormone levels in the blood and on uptake of hormones as drugs (Fournier, Prud'homme, Martin, & Kuttenn, 1983).

In the 1980s the focus of investigation gradually shifted to detailed biochemical analyses of metabolic pathways (Gompel et al., 1986). This approach became the hallmark of the Necker group and its members who "migrated" to other institutions. In the late 1980s and early 90s, new laboratory techniques were developed to study the effects of progestins directly on cell lines both cancerous and normal; these suggested that progestins ought to be effective in preventing breast malignancies by confirming the anti-estrogen activity of progestins in breast tissue, especially in primary cultures of normal breast cells (Mauvais-Jarvis, Kuttenn, Malet, & Gompel, 1990; Gompel et al., 1986; Prud'homme et al., 1984; Mauvais-Jarvis, 1989; Mauvais-Jarvis, Kuttenn, & Gompel, 1986; Mauvais-Jarvis, Kuttenn, & Gompel, 1987). Reacting to articles that took issue with their conclusions, the Necker group proposed an increasingly fine-grained analysis of complex cellular and molecular events in the breast induced by sexual hormones (Mauvais-Jarvis, Kuttenn, Gompel, & Benotmane, 1987). They found that progestins produce divergent effects in different experimental systems, explaining some of the foreign data that contradicted their claims. Nonetheless, they held that the experimental systems used by the French—notably use of normal and not malignant breast cells—more closely mimicked actual physiological conditions (de Lignières, 2002). But above all, the Necker group sought to demonstrate that progestin therapy reduced the danger of breast cancer, especially in pre- and perimenopausal women among whom breast cancer is a leading cause of mortality (Fields, Goldstein, Clark, & Sullivan, 1997). This transformed the therapy from one targeting relatively rare mastodynia into a routine therapy for premenopausal women and into a bridge between the contraceptive pill and hormonal replacement therapy for postmenopausal women.

The Necker group promoted systematic progestin therapy for pre- and perimenopausal complaints, however minor (Mauvais-Jarvis & Kuttenn, 1975). It also advocated the systematic use of progestins—the first hormonal contraceptives tested by fertility experts (Watkins, 1998; Marks, 2001)—as contraceptives in women over 40. Mauvais-Jarvis and his collaborators demonstrated that the administration of a norsteroid (lynestrenol) from the 10th to the 25th day of menstrual cycle does indeed provide efficient contraception, especially appropriate for women who have medical reasons to avoid estrogen or who suffer from premenopausal symptoms that respond to progestin therapy (Kuttenn, Moufarège, & Mauvais-Jarvis, 1978; Sitruk-Ware, 1979; Sitruk-Ware & Mauvais-Jarvis, 1980). Consequently progestin treatment offered premenopausal women multiple benefits: contraception, elimination of disturbing symptoms, and correction of imbalance in estrogen–progesterone ratio, a potential stimulus for malignant growths. It was also seen as safe, especially if administered under rigorous medical supervision (Sitruk-Ware, 1986; Mauvais-Jarvis & Gompel, 1989).

The view that hormone therapy promoted women's health and well-being was shared by many French women, including feminists. In France, hormones were perceived not as a threat or means to dominate women's bodies while turning them into life-long consumers, as was the view of many American feminists, but were on the contrary associated with women's empowerment. During the 1960s and 70s while American scientists and women's health advocates were debating the risks of the pill, French women were campaigning for liberalized access to it. The "progressive"—indeed feminist-positive—nature of hormonal therapy was further promoted by the fact that such therapy was much less available in France, as in the UK, than in the US. Consequently French feminist criticism of the medical establishment tended to focus on the indifference of doctors to women's health, as demonstrated by their reluctance to provide women with hormones. To the extent that French feminists criticized the "medicalization" of the female body, their target was childbirth rather than hormones replacement (Delanoë, 2001).[9]

During the 1970s and 80s, progestin treatment for premenopausal symptoms became widely accepted gynaecological practice in France and was, to some extent, disassociated from the Necker research program. For example, Henri Rozenbaum, president of the influential French Association for Studies of Menopause, was not associated with the Mauvais-Jarvis school and disagreed with their view that mastodynia is linked to progesterone deficiency. Nonetheless, Rozenbaum too advocated progestin therapy during the second half of the menstrual cycle for pre- and perimenopausal woman suffering from such symptoms as abundant and irregular bleeding, fibromas, or breast pain (Rozenbaum, 1990).

[9]For a similar argument about how British feminist attitudes to hormones differed from those in the US, see McCrea and Marle (1984).

The popularity of progestin therapy for pre- and perimenopausal women was grounded, to sum up, in its multifunctionality. The progestogen treatment—if successful—liberated women from several benign but often annoying problems and, for some, from fear of breast cancer linked with mastodynia and mastopathies. It also reduced the need for gynaecological surgery. One of the major indications for progestogen prescription in premenopausal women is precisely the symptoms—uterine fibromas, endometrial hyperplasia, hypermenorrhea, metrorrhagia—that lead to a high proportion of hysterectomies in women over 40 in the USA. Finally it provided efficient contraception at an age when fertility is low but existent without the risks associated with estrogen-based contraception. Progestin treatment also made scientific sense for gynaecologists. The observation that endometrial and breast syndromes frequently appear together reinforced the argument that both events have a common underlying cause—the reduction of progesterone secretion by the corpus luteum during premenopause. However, before doctors—and patients—adopt a therapy, they need to be aware of its existence.

Spreading the views of the Necker School

Many gynaecologists trained in France in the 1980s attest in private conversation to the influence of the Necker group in shaping their views about the clinical benefits of progestins. Mauvais-Jarvis had significant stature in the French medical milieu, and he and members of his team published prolifically and in a wide variety of publications. The group built its scientific reputation on articles published in prestigious endocrinology journals, which established its status within the international field of research on hormone mechanisms. It also published in major English-language medical periodicals like the *British Medical Journal* and *British Cancer Journal*, and Mauvais-Jarvis was invited to be co-editor of an English volume on progesterone and progestins and for which he wrote an introduction (de Lignières et al., 1986; Plu-Bureau, Thalabard, Sitruk-Ware, Asselain, & Mauvais-Jarvis, 1992; Plu-Bureau, Lê, Sitruk-Ware, Thalabard, & Mauvais-Jarvis, 1994; Mauvais-Jarvis, 1982a). Several members of the team moved on from Necker to other prestigious Parisian institutions, including the Institut Gustave Roussy and the Hôtel Dieu Hospital, where they continued research on progestins.

Mauvais-Jarvis also shared his ideas with obstetrician–gynaecologists in the major French journal in that specialty which, at the time, rarely published papers on such issues as menopause or progestins (Mauvais-Jarvis, Sterkers, Kuttenn, & Beauvais, 1978; Mauvais-Jarvis, 1985b). This latter strategy was critical because many of those trained in obstetrics–gynaecology have ended up practicing only gynaecology (by one account, close to half of those who have been trained in the combined specialty now practice gynaecology exclusively (Chanavaz-Lacheray & Nizard, 2003)). Simultaneously, the Necker group moved beyond the restricted circle of medical researchers. Mauvais-Jarvis was one of the two editors of *Lettre de Gynécologie* (founded 1984), a publication sponsored by the pharmaceutical industry and widely diffused among practitioners. He and his colleagues systematically presented their findings to the wider profession in such general medical journals such as *La Presse Médicale* and *Revue du Practicien* (Sitruk-Ware & Mauvais-Jarvis, 1983; Mauvais-Jarvis, 1985a, 1986; Mauvais-Jarvis, Lecomte, & Kuttenn, 1977; Elkik & Mauvais-Jarvis, 1980). The appeal to general practitioners was indispensable since many women in France—especially outside large cities—see GPs for routine gynaecological care.[10]

Mauvais-Jarvis was the first author of the major French collective textbook in medical endocrinology, published in 1982 and reissued with new material in 1986 and 1997. The chapters on premenopause, benign breast disease, endometrial pathologies, or hormones and the breast, were written by members of the Necker group and recommended progestins for a variety of disorders (Mauvais-Jarvis, Sitruk-Ware, & Fabre, 1982; Mauvais-Jarvis, Schaison, & Touraine, 1997). Other books with similar orientation written by members of the Necker School were published in a prestigious series, Flammarion Médecine-Sciences, directed by Mauvais-Jarvis and the popular "101" series of Hachette (de Lignières, 1986; Mauvais-Jarvis et al., 1986; de Lignières, 1979). Mauvais-Jarvis (1977, 1978b, 1979b, 1980, 1981, 1982b), regularly published articles in the medicine section of France's premier newspaper, *Le Monde*. All these publications contributed to the consolidation of the "luteal insufficiency" hypothesis and to the use of progestin therapy for a wide range of disorders.

During the 1980s, progestin therapy became increasingly viewed by French doctors as part of routine management of premenopausal women, akin to HRT therapy for menopausal ones. At the same time, however, the "luteal insufficiency" hypothesis developed by the Necker school came under attack inside France. One of its outspoken opponents was none other than

[10]According to Virginie Ringa, the patterns of prescription of progestins by general practitioners and by gynecologists in the Gazel cohort were identical, suggesting that this strategy was effective. V. Ringa, communication in "Witness Workshop" on progestogens, June 10, 2003. Our data on the Bouches du Rhône also indicate that generalists accounted for close to half of the prescriptions for progestins in April of 2003. In smaller, less urban, departments of the southwest, the figure is considerably higher.

Albert Netter. In 1966, Netter reiterated his earlier view that mastodynia was primarily a psychosomatic disorder. Systematic measurement of hormonal levels in women with mastodynia, he claimed, did not reveal progesterone insufficiency, and in many cases non-hormonal therapy provided better results than progestins (Gorins & Netter, 1966). He confirmed these results in later studies (Netter, 1976, p. 179; 1981a, p. 131). Despite his general enthusiasm for progestin therapy, Henri Rozenbaum (1981) similarly claimed that the available data did not suggest the existence of a single hormonal pattern in mastodynia or mastosis (1981).

Critics like Netter (then long retired) or Rozenbaum and others, whose scientific status did not equal that of Mauvais-Jarvis, probably carried limited weight in the French medical milieu. Objections raised by other endocrinologists could not be so easily ignored. Some French researchers, like the Montpellier-based Henri Rochefort and Thierry Maudelonde, offered more cautious evaluations of the "luteal deficiency" hypothesis. They reminded readers that the protective role of progesterone for the breast was not proven and that these substances induce mammary cancers in animal models. Different studies produced contradictory results, they suggested, perhaps because the clinical definitions of mastodynia or mastopathy are highly variable making it complicated to gather reliable data. In addition, the complexity of hormonal regulation in breast tissue makes experimental studies of anti-estrogenic mechanisms difficult and hard to interpret (Rochefort, 1982; Rochefort & Maudelone, 1989). Several foreign studies also failed to confirm the "luteal deficiency" hypothesis (Swain, Hayward, & Bulbrook, 1973; Malarkey, Schroeden, Stevens, James, & Kanese, 1977; England, Skinner, Cottrell, & Sellwood, 1975).

The elusive epidemiological proof

In France, the Necker team's studies were mainly criticized by investigators who accepted the basic structure of its research but were unable to corroborate the existence of specific hormonal profiles characteristic of mastodynia or pre-menopausal conditions. It was also possible to disagree from the perspective of a totally different research style as did the American endocrinologists who viewed animal experimentation as essential. But the most basic challenge to the views of the Necker group had to do with demonstrating therapeutic efficacy.

Admission of new drugs on the French market required elaborate procedures that focused on determining toxicity, conditions of production and, so far as efficacy was concerned, testing and observation by individual experts (Chauveau, 1999). Through these procedures, progestins were authorized for use in France. However, much of the western medical world had by the early 1980s become convinced that more rigorous testing, notably large, randomized, double-blind trials (RCTs) were necessary to demonstrate conclusively therapeutic efficacy. This idea was slow to take effect in France, but Mauvais-Jarvis and his colleagues, who published regularly in English-language journals, were well aware of these new imperatives and sought to fulfil them. However in the French context of limited funding for clinical testing before France was forced in 1993 to accept European regulations on the introduction of new drugs,[11] such work was difficult. Epidemiological studies—especially prospective ones—were costly, seen as low priority, and complicated by the indeterminacy of breast complaints and the great heterogeneity of prescription practices in France (Gompel et al., 1999; Malet, Spritzer, Guillamin, & Kuttenn, 2000). Since these drugs were already on the market, pharmaceutical companies had little incentive to test them further.[12] The only justification for further testing was the desire of researchers to establish scientifically the soundness of their theories and the efficacy of practices.

In the mid-1980s, the Necker group launched epidemiological investigations to test their assumptions. The scope of these investigations was, however, limited. All were retrospective, case-controlled studies and all were relatively small (the biggest included a little over one thousand cases). Two studies established possible links between mastalgia and later development of breast cancer, strengthening the hypothesis that mastalgia may be a marker of the breast's susceptibility to estrogen at the cellular level. Nonetheless, the authors recognized that small sample size and use of a retrospective method left open the possibility of bias (Sitruk-Ware, Thalabard, Benotmane, & Mauvais-Jarvis, 1989; Plu-Bureau, et al., 1992). Two other retrospective, case-controlled studies (one unpublished) attempted to relate progestin treatment of mastalgia to the incidence of breast cancer and were unable to find statistically significant differences between control and experimental groups; this led to the bland conclusion that progesterone does not *increase* risk of breast cancer. All these studies suffered from small sample size, heterogeneous composition of the subject group, and difficulty providing long-term follow up of women in the cohort (Plu-Bureau et al., 1994)[13].

In the absence of decisive epidemiological proof, the conviction that progestins exercise a protective effect on

[11]The Agence Française de Médicament was established in 1993 and was replaced in 1998 by another agency, AFSSAPs.

[12]The Necker Group did however obtain modest funding for its epidemiological studies from Organon, the producers of Orgametril, a popular progestogen.

[13]Monique Lê, data presented at "Witness workshop" (see endnote 3).

the breast continued to be based on biochemical data. A programmatic paper that carefully summarized the literature on the effects of progestins on breast tissue freely recognized that only RCTs using placebos can provide definitive proof of the benefits of progestogen therapy, but concluded nevertheless "that all the biological activities of progestins indicate in the same direction: a favourable effect on the mammary gland and on cellular transformation" (Gompel et al., 1999, p. 50). Given the symptomatic relief progestins seemed to provide, as well as the belief that their beneficial physiological effects would eventually be proven statistically, it seemed to many gynaecologists prudent on humanitarian grounds to continue prescribing these substances and promoting their use.

Conclusion

Progestins are now widely prescribed in France by general practitioners as well as gynaecologists. We have suggested that this practice grew out of the research of the Necker group which gained wide scientific credibility. The evidence presented by the group was suggestive but not conclusive. Even before the mid-1980s, when epidemiological data became an evidentiary requirement for demonstrating therapeutic efficacy, the physiological research which justified progestin therapy was not convincing to everyone, even on its own terms. Some of this disagreement reflected different styles of physiological research but much of it had to do with inability to confirm the association of luteal insufficiency with pre-menopausal problems. However, this underdetermined evidence did not deter doctors from adopting this therapy. In fact, one could plausibly argue that this is a rather common feature of medical practice.

French doctors were hardly unique in embracing a hopeful if not fully proven therapy. They had better reasons than most to try something recommended in numerous publications by leading medical specialists. They were able to "do" something for their patients while at the same time utilizing their skills in therapeutic judgment to "individualize" therapy, to use just the right products and in just the right combinations. The fact that progestins appeared in most cases to have few negative effects and that these were not life-threatening conditions, made the agents that much easier to prescribe. Criticisms of the luteal insufficiency hypothesis were couched in physiological rather than clinical terms and were usually buried in specialized journals that were not relevant to practitioners. Moreover, critics seldom suggested that these products were actually dangerous. The French themselves were in a position to do only small-scale epidemiological research and the fact that the practice was so uniquely French meant that there was relatively little foreign research that might call it into question.

It is illuminating to compare the case of progestins for pre-menopausal conditions in France with post-menopausal hormone replacement therapy in the US. Like the former, the latter was embraced broadly and enthusiastically during the 1990s by both doctors and their women patients but with important differences. First, despite the widespread enthusiasm, many American women's groups had strong reservations about hormones going back to the early controversies over oral contraceptives (Watkins, 1998; Tone, 2001). Not only was there a constituency that believed that hormones were dangerous, but many women associated these products with the "medicalization" of women's bodies by a paternalistic medical profession and rapacious pharmaceutical industry (Seaman & Seaman, 1977). In contrast, the early identification in France of hormones with the battle to legalize contraception, as well as with the specialty of medical gynaecology, increasingly practiced by women, provided hormones with a benign and even empowering aura. Despite the reservations and indeed hostility of many American feminists, HRT spread even more widely in the US than in France; nonetheless, feminist criticisms were not without influence. They put women's health on the government's research agenda and budget through the Women's Health Initiative (WHI) and made *risk* to women a prevalent concern in the US.

The publication, in 2002, of data from the WHI trial, the first large scale, randomized, controlled study of HRT done in the USA, and then the observational data from the British Million Women Study (MWS), confirmed earlier claims that long term (more than 5 years) intake of menopausal hormonal therapy increased breast cancer risk (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). In fact, it was argued that progestins added significantly to the risk of estrogen alone. Unlike previous research, WHI data indicated that HRT did not diminish—and possibly even increased—cardiovascular risk (WHI, 2002; MWS, 2003). While the number of critics of these conclusions in the US is increasing, the overwhelming tendency at present is to revise therapeutic routines.

In France, reaction has been more mixed. The state agency responsible for regulating drugs and protecting the health of the public (or as some cynics might suggest, protecting the government from charges that it is not doing enough), Agence française de sécurité sanitaire des produits de santé (AFSSAPS), chose the route of caution. It quickly issued a recommendation to doctors to limit HRT to a maximum of 5 years, to be used exclusively for menopause-linked complaints that cannot be controlled with other drugs (Nau, 2003; Benzadon, 2003a). In contrast, practicing gynaecologists, endocrinologists and many epidemiologists have

been critical of these recommendations (Gorins, 2003) arguing that the US data cannot be applied to France for several reasons.

1. The products tested are not used in France where they are recognized to have serious side effects. French gynaecologists, in contrast, prescribe a wide array of other substances and tinker with molecules and doses in order to adapt HRT to the physiological profile of each woman. They also carefully assess the physiological effects of each molecule through in vitro experimentation, clinical observations, and breast and uterine biopsies.

2. The mode of use is different. All the women enrolled in WHI took an oral combination of estrogens and progestins. French women use mainly estrogen patches or, more rarely, gels and nasal sprays, in combination with progestogen pills. The absorption of estrogens via the skin bypasses the liver, reducing the risk of proliferative effects on breast tissue. North American doctors ordinarily prescribe a continuous intake of progestins, while the French doctors have a preference for discontinuous, cyclic administration (Porch, Lee, Cook, Rexrode, & Burin, 2002). Both of these objections have been met to some extent at least by the Million Women's Study which included products that are in current use throughout Europe (Rochefort & Sureau, 2003). But this is not an RTC and is criticized on methodological grounds.

3. French critics have highlighted other issues as well, particularly the advanced average age of the women who participated in the WHI study.[14]

The arguments employed to sustain the claim that there is no need to limit HRT to 5 years—different molecules, different women, different doses and mode of administration, better gynaecological supervision, evidence derived from biochemical studies in cell culture and from investigation of proliferation indexes in surgical biopsies from normal human breast tissue—are very similar to those employed to justify progestin use for premenopausal women (de Lignières, 2002). Frequently, they are advanced by exactly the same people. The tide of medical opinion may or may not change as a result of a new report produced for the prestigious Academy of Medicine that cautiously supports restrictions on use while calling for a European RCT (Rochefort & Sureau, 2003). But in the meantime French and North American women—as well as their doctors—have reacted very differently to news about HRT risk. In 2003, there was a sharp (more that 50%) decrease in HRT prescriptions in the USA (Ettinger, Grady, Tosteson, Pressman, & Macer, 2003; Hersch, Stefanick, & Stafford, 2004); in France, in contrast, only 19% of women decided to stop HRT use, and one-quarter of these eventually went back to this therapy in diminished doses (Andre, 2003).

The story of HRT is closely related to the progestin story discussed in this paper. Foreign studies of HRT, in the absence of more direct evidence, constitute the most convincing available argument that risks may be associated with pre-menopausal progestin therapy. In fact, these studies are constructed in such a way as to cast doubt on or simply ignore the French assumption that the boundary between treatment for pre- and post-menopausal women constitutes a rather fuzzy continuum. It is likely that the future of progestin therapy for pre-menopausal women in France will be decided ultimately by local perceptions of the dangers of post-menopausal hormone therapy.

The growing influence of evidence based medicine in France does not seem—for the moment—to have eliminated local variance in practices. This should not surprise us. Doctors and patients function in specific cultural milieus. Research styles differ as do the socio-political contexts in which these styles operate. Even within the epidemiological research style which claims superiority over all others for evaluating risk and efficacy, results are frequently inconclusive enough to permit multiple readings of the evidence and these readings are inevitably informed by prior scientific, cultural and political commitments. Perhaps, then, it is our quest for uniformity that requires closer examination.

[14]These arguments summarize communications presented at a meeting, "HRT and Cancer" sponsored by the French Society for the Study of Cancer, held at the Curie Institute, May 15, 2003. Guy Benzadon (2003b).

Acknowledgements

We are grateful for the help we received from everyone who participated in the "Witness seminar on progestins, Paris, June 10, 2003". We express special thanks to Anne Gompel, Henri Rochefort, Beatrice Jacqueme, Monique Lê, Bruno de DeLignieres, J.C. Thalabard, Virginie Ringa, and Sophie Chauveau.

References

Agence française de sécurité sanitaire des produits de santé: Direction des Etudes Médico-Economiques et de l'Information Scientifique (2002). Analyse des ventes de médicaments aux officines et aux hôpitaux en France 1988–2000, Octobre 2002; Tableau 2: Les cinquante produits les plus vendus en officine en 2000. In http://agmed.sante.gouv.fr/htm/5/5000.htm.

Andre, M. (2003). L'impact de WHI sur les femmes. *Quotidien de Médecin*, *December 12*.

Bar, P. (1911). Évolution de l'Obstétrique en France. *L'Obstétrique*, *16*, 1–23.

Béclère, C. (1951). Aménhorrhée primitive à 25 ans: Etablissement des règles par une dose unique faible de

folliculine-progestrone. *Comptes Rendus de la Société franç aise de Gynécologie*, *21*, 375.

Béclère, C. (1954). Fibrome sous-muqueux traité par la testosterone pendant 6 ans puis par la reontgenthérapie. *Comptes Rendus de la Société française de Gynécologie*, *24*, 330.

Benzadon, G. (2003a). L'Afssaps restreint ses indications. *Quotidien du Médecin*, *December 5*.

Benzadon, G. (2003b). Les spécialistes de la ménopause en désaccord partiel avec l'afssaps. *Quotidien de médecin*, *December 11*.

Berlivet, L. (2000). *Une santé à risque*: *L'action publique de lutte contre l'alcoolisme et le tabagisme en France*, 1954–1999. PhD dissertation, Univeristy of Rennes.

Bernard, I. (1960). Sur les norsteroïdes progestatifs. *Bulletin de la Fédération des Obstétriciens et des Gynécologues de la Langue Française*, *12*, 57–59.

Chanavaz-Lacheray, I., & Nizard, J. (2003). Les internes de gynécologie obstétrique français et européens s'opposent au project de DES de gynécologie médicale français. *Journal de Gynécologie, Obstetrique et Biologie de la Reproduction*, *32*, 268.

Chauveau, S. (1999). *L'invention pharmaceutique: la pharmacie française entre l'Etat et la société au XXe siècle*. Paris: Sanofi-Synthélabo.

Chaveau, S. (2003). Les espoirs deçus de la loi Neuwirth. *Clio*, *18*, 223–239.

Collaborative Group on Hormonal Factors in Breast Cancer (1997). Breast cancer and hormone replacement therapy: collaborative reanalysis from 51 epidemiologic studies on 52705 women with breast cancer and 108411women without breast cancer. *Lancet*, *350*, 1047–1059.

Comptes Rendus de la Société française de Gynécologie, *9* (1939).

Conseil National de l'Ordre des Médecins (1985). Les médecins spécialistes en France, *Etudes démographiques*, *12*, 15–16.

Dalton, K. (1959). Comparative trial of new oral progestogenic compounds in treatment of premenstrual syndrome. *BMJ*, *ii*, 1307–1309.

Dalton, K. (1984). *The premenstrual syndrome and progesterone therapy* (2nd ed.). Chicago: Yearbook Medical Publishers.

Daurand (1958). La spécialisation. *Concours méd*., 3095–3106.

Debuc, M. (1949). Sur un cas de hypertrophie de la vulve traitée par la propionate de testosterone. *Comptes Rendus de la Société française de Gynécologie*, *19*, 220.

Delanoë, D. (2001). *Critique de l'âge critique, usage et représentations de la Ménopause: Thèse d'anthropologie sociale et ethnologie*. Paris: EHESS.

de Lignières, B. (1979). *101, La ménopause*. Paris: Hachette.

de Lignères, B. (1986). *Les syndromes prémenstruels*. Paris: Flamarion Medecine-Sciences.

de Lignières, B. (2002). Effects of progestogens on the postmenopausal breast. *Climacteric*, *5*, 229–235.

de Lignières, B., Vincens, M., Mauvais-Jarvis, P., Mas, J. L., Touboul, P. J., & Bousser, M. G. (1986). Prevention of menstrual migraine by percutaneous oestradiol. *BMJ (Clinical Research Edition)*, *293*(6561), 1540.

Elkik, F., & Mauvais-Jarvis, P. (1980). Rôle de la progesterone et des progestatifs sur le métabolisme hydroélectrolytique. *La Nouvelle Presse Médicale*, *9*(1), 35–38.

England, P. C., Skinner, L. C., Cottrell, K. M., & Sellwood, R. A. (1975). Sex hormones in breast disease. *British Journal of Surgery*, *62*, 806–809.

Ettinger, B., Grady, D., Tosteson, A. N. A., Pressman, A., & Macer, J. L. (2003). Effect of the womens' health initiative on women's decision to discontinue postmenopausal hormone therapy. *Obstetrics and Gynecology*, *102*(6), 1225–1232.

Fields, K., Goldstein, S., Clark, R., & Sullivan, D. (1997). Breast cancer. In B. Djulbegovi, & D. M. Sullivan (Eds.), *Decision making in oncology* (pp. 253–265). New York: Churchill Livingstone.

Fournier, S., Prud'homme, J. F., Martin, P. M., & Kuttenn, F. (1983). Recepteurs des hormones steroides dans les maladies bénignes du sein. *Pathologie Biologique*, *31*(9), 767–773.

Gompel, A., Chaouat, M., Jacob, D., Perrot, J.Y., Kloosterber, H.J., & Rostene, W. (1999). Les progestatifs ont-il une place dans la prevention? In Lefranc, J. P., Rouësse, J., Tristant, H., & Villet, R. (Eds.). *Cancer du sein: Controverses et convergances* (pp. 38–52). Paris: Armett.

Gompel, A., Malet, C., Spritzer, P., Lalardrie, J. P., Kuttenn, F., & Mauvais-Jarvis, P. (1986). Progestin effect on cell proliferation and 17 beta-hydoroxysteroid dehodrogenase activity in normal human breast cells in culture. *Journal of Clinical Endocrinological Metabolism*, *63*(5), 1174–1180.

Gorins, A. (2003). Progestins and risk of breast cancer: much ado about nothing? *European Journal of Gynaecological Oncology*, *24*(5), 345–350.

Gorins, A., Netter, A. (1966). Etude hormonale des mastoses. In Les mastopathies (cancers et infections exceptés): XXIIIe Assises françaises de gynécologie, Bordeaux, 19 au 22 mai, 1966, ed. P. Gautier, (pp. 149–190). Paris: Masson.

Greene, R., & Dalton, K. (1953). The premenstrual syndrome. *BMJ*, *i*, 1–14.

Hainaux, H. (1965). Résultats de notre expérience dans le traitement des fibromes par les progestatifs de synthèse. *Comptes Rendus de la Société française de Gynécologie*, *35*, 416.

Hersh, A. L., Stefanick, M. L., & Stafford, R. S. (2004). National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA*, *291*(1), 47–53.

Kuttenn, F., Martin, P. M., & Mauvais-Jarvis, P. (1979). Le risque hormonal et les mastopathies. *Senologia*, *4*(4), 250–256.

Kuttenn, F., Moufarège, A., & Mauvais-Jarvis, P. (1978). Bases hormonales de la contraception progestative discontinue. *La Nouvelle Presse Médicale*, *7*(35), 3109–3113.

Lambert, A., & Netter, A. (1956). Les mastopathies endocriniennes ou soi-disant telles. *Revue de Practicien*, *6*, 1018–1049.

Lefaucher, N. (1988). La résistible création des accoucheurs des hôpitaux. *Sociologie de Travail*, *30*, 323–352.

Love, S. M., Gelman, R. S., & Sleen, W. (1982). Fibrocystic disease of the breast: a non-disease. *NEJM*, *307*, 1010–1012.

Malarkey, W. B., Schroeden, L. L., Stevens, V. C., James, A. G., & Kanese, R. R. (1977). Twenty four hours preoperative hormone profile in women with benign and malignant breast disease. *Cancer Research*, *37*, 4655–4659.

Malet, C., Spritzer, P., Guillamin, D., & Kuttenn, F. (2000). Progesterone effect on cell growth ultrastructural aspect and estradiol receptors of normal human breast epithelial cells in culture. *Journal of Steroid Biochemistry and Molecular Biology*, *73*(3–4), 171–182.

Marcel, J. E. (1948). Comment devenir gynécologue. *Comptes Rendus de la Société française de Gynécologie*, *18*, 183.

Marks, L. (2001). *Sexual chemistry: the history of the contraceptive pill*. Princeton: Princeton University Press.

Mauvais-Jarvis, P. (1972). Données thérapeutiques actuelles concernant les mastodynies et les mastophaties benignes. *Annales d'Endocrinologie*, *33*, 78–79.

Mauvais-Jarvis, P. (1975). Mastopathies bénignes et cancer du sein. *La Revue de Practicien*, *25*(37), 2879–2884.

Mauvais-Jarvis, P. (1977). La menopause, un traitement bien adapté. *Le Monde*, *June 8*.

Mauvais-Jarvis, P. (1978a). Interprétation hormonale de l'épidémiologie de cancer de sein. *Le Journal des Agrégés*, *12*(4), 285–294.

Mauvais-Jarvis, P. (1978b). Tumeurs de sein. Hauts risques et prevention. *Le Monde*, *November 22*.

Mauvais-Jarvis, P. (1979a). De l'hormonologie des mastopathies à la prevention du cancer du sein. *La Nouvelle Presse Médicale*, *8*(22), 1817–1819.

Mauvais-Jarvis, P. (1979b). Plaidoyer pour une gynécologie moderne. *Le Monde*, *March 7*.

Mauvais-Jarvis, P. (1980). La médecine de la réproduction: Une nouvelle spécialité. *Le Monde*, *June 11*.

Mauvais-Jarvis, P. (1981). Rôle physiologique de L'equilibre esterprogestatif. *La Revue du praticien*, *31*, 1391–1395.

Mauvais-Jarvis, P. (1982a). Introduction: progesteron and progestins. A general overview. In C. Wayne Bardin, E. Milgrom, & P. Mauvais-Jarvis (Eds.), *Progesterone and progestins*. New York: Raven Press.

Mauvais-Jarvis, P. (1982b). Minipillule et pillule normodosé. *Le Monde*, *February 10*.

Mauvais-Jarvis, P. (1985a). Mastopathies bénignes et cancérogénèse mammaire: une réactualisation. *Presse Medicale*, *14*(30), 1585–1586.

Mauvais-Jarvis, P. (1985b). Pourquoi traiter médicalement les mastopathies bénignes. *Journal of Gynecology Obstetrics Biology Reproduction*, *14*, 623–626.

Mauvais-Jarvis, P. (1986). L'endocrinologie à l'heure de la réceptivité hormonale. *Presse Medicale*, *15*(34), 1705–1707.

Mauvais-Jarvis, P. (1989). Antiestrogènes et proliferation cellulaire mammaire normale humaine. *Annales d'Endocrinologie*, *50*, 181–188.

Mauvais-Jarvis, P., & de Lignières, B. (1976). Hypothèses sur l'épidémiologie hormonale du cancer du sein. *Actualités Gynecologiques (Paris: Masson)*, *7*, 223–227.

Mauvais-Jarvis, P., & Gompel, A. (1989). *Hormones et sein*. Paris: Flammarion Médecine-Sciences.

Mauvais-Jarvis, P., & Kuttenn, F. (1974). Les mastophies benignes: pathologie méconnue. *Nouvelle Presse Médicale*, *3*(16), 993–994.

Mauvais-Jarvis, P., & Kuttenn, F. (1975). L'insuffisance en progestérone est-elle carcinogène? *La Nouvelle Presse Médicale*, *4*(5), 323–326.

Mauvais-Jarvis, P., Kuttenn, F., & Gompel, A. (1986). Estradiol/progesterone interaction in normal and pathological breast cells. *Annals of the New York Academy of Sciences*, *464*, 152–167.

Mauvais-Jarvis, P., Kuttenn, F., & Gompel, A. (1987). Antiestrogen action of progesterone in breast tissue. *Hormones Research*, *28*(2–4), 212–218.

Mauvais-Jarvis, P., Kuttenn, F., Gompel, A., & Benotmane, A. (1987). Actions anti-estrogène de la progesterone dans le sein. *Pathobiology*, *35*(7), 1081–1086.

Mauvais-Jarvis, P., Kuttenn, F., Malet, C., & Gompel, A. (1990). Normal breast cells in culture: effect of estrogens, progestins, and antiestrogens. *Annals of the New York Academy of Sciences*, *595*, 117–129.

Mauvais-Jarvis, P., Kuttenn, F., & Ohlgiesser, C. (1974). Résultats du traitement de mastodynies et de mastopathies par la progestèrone percutanée. *La Nouvelle Presse Médicale*, *3*(16), 1027–1028.

Mauvais-Jarvis, P., Kuttenn, F., & Wright, F. (1975). Progesterone administré par la voie percutané. *Annales d'Endocrinologie*, *36*(2), 55–62.

Mauvais-Jarvis, P., Lecomte, P., & Kuttenn, F. (1977). La gynécologie endocrinienne en 1977. *Revue Du Praticien*, *27*(17), 1011–1029.

Mauvais-Jarvis, P., Schaison, G., & Touraine, P. (1997). *Médecine de la reproduction: Gynécologie endocrinienne* (3rd ed.). Paris: Flammarion.

Mauvais-Jarvis, P., Sitruk-Ware, R., & Fabre, L. (1982). *Médecine de la reproduction: Gynecologie endocrinienne*. Paris: Flammarion.

Mauvais-Jarvis, P., Sitruk-Ware, R., Kuttenn, F., & Sterkers, N. (1979). Luteal phase insufficiency: a common physiological factor in the development of benign and malign breast diseases. In R. D. Bulbrook, & J. Taylor (Eds.), *Commentaires on research on breast disease* (pp. 25–59). New York: Alan Liss.

Mauvais-Jarvis, P., Sitruk-Ware, R., Sterkers, N., & Moszowicz, I. (1977a). Inadequate corpus luteum function in women with benign breast disease. *Journal of Clinical Endocrinology & Metabolism*, *44*, 771–780.

Mauvais-Jarvis, P., Sterkers, N., Kuttenn, F., & Beauvais, J. (1978). Traitement des mastopathies bénignes par la progesterone et les progestatifs. *Journal of Gynecology Obstetric Biology Reproduction*, *7*(3), 477–484.

McCrea, F. B., & Marle, G. E. (1984). The estrogen replacement controversy in the USA and UK: different answers to the same question? *Social Studies and Science*, *14*, 1–26.

Million Women Study Collaborators (2003). Breast cancer and hormone-replacement therapy in the Million Woman Study. *The Lancet*, *362*, 419–427.

Moscucci, O. (1990). *The science of woman: gynaecology and gender in England, 1800–1929*. Cambridge: Cambridge University Press.

Nau, J. Y. (2003). Cancer du sein, durée maximale du traitement et alternatives médicamenteuses. *Le Monde*, *February 9–10*.

Netter, A. (1960). Thérapeutique du syndrome prémenstruel. *Entretiens de Bichat*, 146–147.

Netter, A. (1976). La prémenopause: etude hormonale et traitement. *Actualités Gynécologiques*, *7*, 171–181.

Netter, A. (1981a). Mastopathies benignes et l'état hormonal. *Actualités Gynecologiques*, *12*, 127–132.

Netter, J. A. (1981b). *Vaincre sa menopause*. Paris: Albin Michel.

Papers presented at a "witness workshop" on progestogens, Paris, June 10, 2003.

Payer, L. (1947). Influence de la technique chirurgicale sur le choc opératoire en gynécologie. *Comptes Rendus de la Société française de Gynécologie*, *17*, 89–95.

Payer, L. (1988). *Medicine and culture: varieties of treatment in the United States, England, West Germany and France*. New York: Henry Holt.

Pike, M. C., Krailo, M. D., Henderson, B., Casagrande, J. T., & Hoel, D. G. (1983). Hormonal risk factors, breast tissue age and the age-incidence of breast cancer. *Nature*, *303*, 767–770.

Plu-Bureau, G., Lê, M. G., Sitruk-Ware, R., Thalabard, J. C., & Mauvais-Jarvis, P. (1994). Progestogen use and decreased risk of breast cancer in a cohort study of premenopausal women with benign breast disease. *British Journal of Cancer*, *70*(2), 270–277.

Plu-Bureau, G., Thalabard, J. C., Sitruk-Ware, R., Asselain, B., & Mauvais-Jarvis, P. (1992). Cyclical mastalgia as a marker of breast cancer susceptibility: results of a case-control study among French women. *British Journal of Cancer*, *65*(6), 945–949.

Porch, J. V., Lee, I.-M., Cook, N. R., Rexrode, K. M., & Burin, J. E. (2002). Estrogen–progestin replacement therapy and breast cancer risk: the Women Health Study (United States). *Cancer Causes and Control*, *13*, 847–854.

Prud'homme, J. F., Malet, C., Gompel, A., Lalardie, L. P., Boue, A., Mauvais-Jarvis, P., & Kuttenn, F. (1984). 17ßhydroxystroid dehydrogenase activity in human breast epitelioma and fibroblasts in cultures. *Endocrinology*, *114*, 1483–1489.

Ringa, V., Legare, F., Dodin, S., Norton, J., Godin, G., & Breart, G. (2004). Hormone therapy prescription among physicians in France and Quebec. *Menopause*, *11*(1), 89–97.

Rochefort, H. (1982). Les antiesterogènes. *Actualités Gynecologiques*, *13*, 97–106.

Rochefort, H., & Maudelone, T. (1989). *Les antioesterogènes*. Paris: Flammarion.

Rochefort, H. & Sureau, C. (2003). Rapport au nom d'un groupe de travail, les traitements hormonaux substitutifs (THS) de la ménopause: evolution récente du rapport bénéfices/risques. December 2 on the website of the Académie Nationale de Médecine.

Rozenbaum, H. (1981). A propos de la pathologie des mastoses et du syndrome premenstruel. *Actualités Gynecologiques*, *12*, 133–141.

Rozenbaum, H. (1982). *Les progestatifs de synthèse*. Paris: Pariente.

Rozenbaum, H. (1990). La perimenopause. In H. Rozenbaum, & J. J. Peumey (Eds.), *Histoire illustré de la ménopause* (pp. 203–213). Paris: Editions Roger Dacosta.

Ruf, H., Coddacione, J. L., & Gernent, H. (1964). Le norethynodrel dans le syndrome premenstruel et les dysplasies mammaires. *Bulletin de la Fédération des sociétés de gynécologie et d'obstétrique de langue française*, *16*, 587–590.

Rautureau, M., & Mardrus, C. (1950). La folliculine, antiabortive. *Comptes Rendus de la Société française de Gynécologie*, *20*, 208.

Sappey, P. (1946). La castration est une défaite: nécessité des traitements gynécologiques prolongés avant toute intervention. *Comptes Rendus de la Société française de Gynécologie*, *16*, 55–61.

Seaman, B., & Seaman, G. (1977). *Women and the crisis in sex hormones*. New York: Rawson.

Serafino, X. (1946). Les perturbations fonctionnelles de l'ovariectomie unilatérale. *Comptes Rendus de la Société française de Gynécologie*, *16*, 93–96.

Sherman, B. M., & Korenman, S. G. (1974a). Inadequate corpus luteum function in women with benign breast disease: a physiopathological interpretation of human breast cancer epidemiology. *Cancer*, *33*, 1306–1312.

Sherman, B. M., & Korenman, S. G. (1974b). Measurement of serum LH, FSH, estadriol and progesterone in disorders of human menstrual cycle: the inadequate luteal phase. *Journal of Clinical Endocrinology & Metabolism*, *39*, 145–149.

Sitruk-Ware, R. (1979). *La ménopause*. Laboratoires Besins-Iscovesco.

Sitruk-Ware, R. (1986). *La ménopause*. Paris: Flammarion Médecine-Sciences.

Sitruk-Ware, R., & Mauvais-Jarvis, P. (1980). Faut–il traiter la ménopause. *La Revue de Médecine Thérapeutique*, *35*, 1795–1803.

Sitruk-Ware, R., & Mauvais-Jarvis, P. (1983). Les progestatifs. *Presse Medicale*, *12*(25), 1601–1605.

Sitruk-Ware, R., Thalabard, J. C., Benotmane, A., & Mauvais-Jarvis, P. (1989). Risk for breast cancer fibroadenoma in young women. *Contraception*, *40*(3), 251–268.

Swain, M. C., Hayward, J. L., & Bulbrook, R. D. (1973). Plasma œstradion and progesterone in benign breast disease. *European Journal of Cancer*, *9*, 553–556.

Tone, A. (2001). *Devices and desires: a history of contraceptives in America*. New York: Hill and Wang.

Ulrich, P. (1948). Note sur le traitement du cancer du sein par l'hormone male. *Comptes Rendus de la Société française de Gynécologie*, *18*, 257–261.

Ulrich, P. (1949). A propos des fractures métastatiques du cancer du sein traitées par les androgens. *Comptes Rendus de la Société française de Gynécologie*, *19*, 84.

Vokaer, R. (1954). *Thérapeutique hormonale en gynécologie et obstetrique*. Paris: Masson et Cia.

Watkins, E. S. (1998). *On the pill: a social history of oral contraceptives, 1950–1970*. Baltimore: The Johns Hopkins University Press.

Weisz, G. (2002). Specialist regulation in France during the first half of the twentieth-century. *Social History of Medicine*, *15*, 457–480.

Weisz, G. (forthcoming). *Divide and conquer*: *a comparative history of medical specialization*. New York: Oxford University Press.

Writing Group for the Women's Health Initiative (WHI) (2002). Risks and benefits of estrogen plus progesterins in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*, *288*, 321–333.

Wyatt, K., Dimmock, P., Jones, P., Obhrai, M., & O'Brien, S. (2001). Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. *BMJ*, *323*, 1–8.

Wyatt, K. M., Dimmock, P. W., Frischer, M., Jones, P. W., & O'Brien, S. P. (2002). Prescribing patterns in premenstrual syndrome. *BMC Women's Health 2*.